Basic Principles of HIV

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HIV Types, Groups, Subtypes and Recombinant Forms: Errors in Replication, Selection Pressure and Quasispecies

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HIV · Quasispecies · Genetic factors · Selection pressure · AIDS

Abstract
HIV-1 is a chimpanzee virus which was transmitted to humans by several zoonotic events resulting in infection with HIV-1 groups M–P, and in parallel transmission events from sooty mangabey monkey viruses leading to infections with HIV-2 groups A–H. Both viruses have circulated in the human population for about 80 years. In the infected patient, HIV mutates, and by elimination of some of the viruses by the action of the immune system individual quasispecies are formed. Along with the selection of the fittest viruses, mutation and recombination after superinfection with HIV from different groups or subtypes have resulted in the diversity of their patterns of geographic distribution. Despite the high variability observed, some essential parts of the HIV genome are highly conserved. Viral diversity is further facilitated in some parts of the HIV genome by drug selection pressure and may also be enhanced by different genetic factors, including HLA in patients from different regions of the world. Viral and human genetic factors influence pathogenesis. Viral genetic factors are proteins such as Tat, Vif and Rev. Human genetic factors associated with a better clinical outcome are proteins such as APOBEC, langerin, tetherin and chemokine receptor 5 (CCR5) and HLA B27, B57, DRB1*1303, KIR and PARD3B.

Origin of the Types and Groups of HIV and Its Epidemiology

HIV-1

HIV is subdivided into two types, HIV-1 and HIV-2. HIV-1 was transmitted to man by at least 4 zoonotic transmissions, groups M–P, of the corresponding chimpanzee virus. This transmission occurred around 1930 (±20 years), estimated from the molecular biological phylogenetic data available [1]. The chimpanzee virus SIVcpz might date back to many thousands of years ago. It is a recombinant virus built up in its gag and pol part from the simian immunodeficiency virus (SIV) of red-capped mangabey monkeys *(Cercocebus torquatus)* and in its env part from SIVgsn or SIVmon of the greater spot-nose monkey *(Cercopithecus nicticans)* or mona monkey *(Cercopithecus mona)*, respectively. SIV-infected chimpanzees in regions of central Africa have evolved to different subspecies *(Pan troglodytes troglodytes* and *P. troglodytes schweinfurthii)*. After the separation of groups of chimpanzees by big rivers, their SIVcpz viruses diverged and only the SIVs of *P. troglodytes troglodytes* chimpanzees seem to be ancestors of the various HIVs. The presence of an HIV-like retrovirus in around 5% of these animals indicates a coevolution of host and virus over a long period of time [2]. In most chimpanzees SIVcpz is apathogenic [3]. SIVcpz was hitherto not found in the chimpanzee subspecies *P. troglodytes vellerosus* and *P. troglodytes verus*.

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As a result of its spread and evolution in man, HIV-1 group M has been subdivided into subtypes A–K, where subtypes E and I are missing since they are circulating recombinant forms (CRF) [1, 4]. According to genetic relatedness there are 2 great lineages in HIV groups, M and N, and O and P. People carrying group N and P viruses are very rare, with, currently in Cameroon, about 20 and 3 infected people, respectively. Group O virus infections are prevalent in about 0.1–1% of the sexually active population in Cameroon; some infected individuals have also been identified in the neighboring countries of Gabon and Equatorial Guinea.

HIV-1 group M has a worldwide distribution with currently more than 35 million infected people. A higher prevalence of all subtypes is found in sub-Saharan Africa, of subtype B in North and South America and Western Europe, of subtype A in Eastern Europe, of subtype C in southern Africa and India and of subtype A/E (CRF01) in southeast Asia [5]. Group M subtype C is worldwide the most prevalent HIV-1, but rare subtypes may occur in all countries.

Diagnostic tools, i.e. tests for antibody detection, viral load measurement and resistance determination, are mainly based on subtype B; this aspect needs to be considered along with the fact that other subtypes are prevalent in certain countries of the world, when tests are interpreted as well in the choice of drugs for patient treatment, i.e. non-nucleoside reverse-transcriptase inhibitors for subtype C.

HIV-2

The origin of HIV-2 is SIVsmm, the SIV of sooty mangabey monkeys *(Cercocebus atys)* in West Africa [6]. Today HIV-2 is divided into the groups A–H, of which A and B are the most prevalent and perhaps the only pathogenic ones. The easiest explanation for the presence of these groups in humans is that the independent and separate zoonotic transmission of a virus of each group to humans and further spread amongst humans by sexual transmission. Calculations of the nucleic acid sequence data estimated the date of introduction of HIV-2 in humans to 1940 (±20 years), which is very close to the predicted introduction of HIV-1 [7]. HIV-2 is less pathogenic than HIV-1, which results in a prolonged period until the signs of immunodeficiency and AIDS develop, and a mother-to-child transmission rate of around 7‰ to 2%, compared to 10–40% in those infected with HIV-1 [8]. The prevalence of HIV-2 in some African communities has reached approximately 10–16% over time, but this is currently being overtaken by HIV-1 [9]. HIV-2 is rare outside of West Africa, Mozambique, Angola and southwest India. A few people might be coinfected with both viruses, and HIV-2 does not induce immunity to prevent HIV-1 superinfection, nor vice versa [10]; doubly infected patients develop an immunodeficiency and all the signs of AIDS earlier. Until now, a recombinant virus composed of parts of HIV-1 and HIV-2 has not been found in humans.

Mutation Rate and Quasispecies

The replication cycle of HIV within the cytoplasm of a susceptible CD4 T lymphocyte, macrophage or dendritic cell starts after entry into the cell and cleavage of the core followed by synthesis of one new DNA strain. The reverse transcriptase (RT) synthesizes the first DNA strain using the viral RNA as a template. After RNA digestion by the RNase activity the RT synthesizes the second complementary strand. Finally, the double-stranded DNA molecule (proviral DNA) is released into the nucleus and integrated into the human host cell genome [11].

The RT part of the polymerase has some enzymatic peculiarities: first, an error-prone activity during RNA-DNA transcription that is combined with a preference to incorporate G in favor of A [12], and second, to jump and attach onto some neighboring nucleic acids so that deletions, and to some extent insertions, occur frequently [12, 13]. The error rate is about 1 in 10,000 nucleotides [13, 14], which means that in each replication cycle in which the reverse transcription is involved, statistically one false nucleotide is incorporated in the HIV genome. Some parts of the 3-dimensional configurations of the enzymes and of structural proteins of HIV are essential for function. These regions are highly conserved, whereas other parts are tolerant to mutations. Examples of highly conserved structures are parts of long-terminal repeats, active enzymatic parts of the RT and integrase and p24 protein parts needed for condensation of the core; examples of hypervariability are parts of the envelope proteins gp120 and gp41, particularly the V3 loop in gp120 [15].

Selection Pressure by Antiretroviral Drugs

The antiretroviral treatment with nucleoside RT inhibitors induces a selection pressure in parts of the RT that are close to the enzymatic pocket in a direction such that the wild-type enzyme is inhibited by the drugs, and thus HIVs carrying wild-type RT are no longer produced. HIV strains with a mutated enzyme that are resistant to the drug will continue to replicate and adapt, and most replicate as fast as the wild-type virus. In a similar way, a mutated HIV strain can escape from the action of the im-

mune system which is favored when random mutations are found in the gp120 protein, especially in the crown of the V3 loop. Usually for the first 5 years after infection, those HIV strains that are not cleared by immune action continue to replicate and will contribute to the HIV quasispecies population found in the sexual and cerebral compartment and in the blood [16, 17].

Finally, there are certain parts of the HIV genome, noncoding (long-terminal repeat) or coding regions for proteins, e.g. accessory proteins, where mutations are tolerated. As a consequence of rapid HIV replication, a cloud of mutated viruses accumulates after the first 6 months in the organism of the HIV-infected person. The formed quasispecies are all still, for example, HIV-1 M subtype B. Some of these members of the HIV quasispecies are eliminated by antiretroviral treatment with a decay half-life time in resting activated CD4 cells and CD14+ monocytes of around 20 months [18]; meanwhile, new HIVs are generated by new mutations and will overgrow and replace the circulating population [16]. This cycle of generation of new quasispecies is ongoing until the AIDS stage is reached, when finally one population becomes dominant and causes severe CD4 cell depletion. The formation of quasispecies is not restricted to HIV but may be seen in other chronic infections with RNA viruses as well, e.g. influenza, hepatitis C and the picornavirus [19, 20].

Recombination

A frequent action of a retrovirus to enlarge its genetic repertoire is the formation of recombinants. When a cell gets infected by two genetically different HIV-1 viruses, the RT may use both RNA templates for the first strand synthesis. As a consequence, a recombinant virus is formed harboring parts of the genome of strain 1 and strain 2. A recombination event in one cell occurs in 1 in 400 HIV particles produced [21, 22]. There might be some regions of preselection where it occurs [22]. Recombination between the different members of a quasispecies, including drug-resistant strains, is a frequent event. A newly formed recombinant HIV might be very stable [23] as is the case for the chimpanzee virus which is the origin of HIV-1, for the CRF01 which is a recombinant of A and E, for CRF02 which is a recombinant of A and G, and for CRF17 which did not change during the 20 years of follow-up in Cameroon [4, 24].

New recombinants occurring after 1990 between different group M subtypes have been found frequently around the world as CRF07 and 08 (BC) in China, CRFF12, 28 and 29 (BF) in Argentina and Brazil, or mixtures of 3 different subtypes [24]. Recombinants between group M and group O have been found in Cameroon. As mentioned above, natural recombinants between HIV-1 and HIV-2 have not been found, despite the fact that these can be formed artificially in the laboratory [24]. Recombination is a frequent event in other RNA viruses, e.g. flavivirus, influenza virus (reassortment) and reovirus [26].

Superinfection

Cellular Level

After entry into a cell, HIV alters the cell metabolism. One of the actions triggered by the Nef protein is the internalization of CD4 molecules expressed on the surface of the cell, accompanied by inhibiting or retarding the transport of newly synthesized CD4 molecules to the cell membrane [27]. By this mechanism, superinfection of an already infected cell with a further HIV is impaired but still continues [28].

Patient Level

Superinfection of an HIV-infected person with a newly acquired HIV, e.g. by sexual transmission, has been observed frequently [29]. The immunity established by the first infecting HIV strain remains incomplete due to viral mutation, which is in turn due to a lack of efficiently neutralizing antibodies and primed CD8 lymphocytes incapable of killing all HIV infected cells, especially those in the sanctuary sites [30, 31]. Thus, a multi-drug-resistant strain is also able to superinfect an HIV-infected patient, and as a result, a multi-drug-resistant HIV profile may be seen during follow-up in a patient who previously had a virus with a susceptible drug profile [23, 32, 33].

Genetic Repertoire Influencing the Replication of HIV

Viral Factors

Several accessory proteins support and accelerate HIV replication which is usually called viral fitness [34]. The most effective of these proteins is Tat, which acts as viral transcriptional transactivator, Rev, which regulates the RNA transport and Vif, which promotes viral maturation and release from the cell. None of these 3 proteins is involved in the formation of drug resistance.

Human Factors

Due to mutations (single nucleotide polymorphism) in the human genome the genetic background is heterogeneous. Proteins involved in the suppression of HIV replication and pathogenesis are: APOBEC3 – an apolipoprotein B mRNA-editing, enzyme-catalytic, polypep-

tide-like 3 enzyme which interferes with Vif [35], langerin – CD 207, a type II transmembrane protein of Langerhans cells in the mucosa and epidermis that binds by a lectin-mannose action to HIV glycoproteins and accelerates internalization and subsequent degradation of the particle [36], tetherin – CD317, a human cellular protein capable of inhibiting HIV replication by interfering with Vpu, catching the freshly released HIV particle at the cell surface and forcing endocytosis and degradation [37] and CCR5 – chemokine receptor 5, which, when lacking at the cell surface, delays lymphocyte attachment of HIV R5 strains that use it as a coreceptor together with the CD4 molecule [36]. The capability of an R5 virus to adhere to the amino acid motif of the V3 loop of gp120 can easily be determined by nucleic acid sequencing and thus the inhibitory capacity of maraviroc, for example, can be determined [39]. Human genetic factors of the immune system that influence progression of the HIV disease are HLA molecules, HLA B27, B5901 and DRB1*1303 [40]. Further genetic factors associated with single nucleotide polymorphism that might be protective or enhancing have been found in PARD3B, RANTES and KIR [41].

Both viral and human genetic factors contribute to HIV pathogenesis and some of the viral factors are routinely identified by nucleic acid sequencing as targets to estimate and improve the outcome of the HIV-infected patient. To analyze human genetic factors besides CCR5, APOBEC and HLA might be a future challenge for those involved in the determination of HIV drug resistance.

References

1 Korber B, Muldoon M, Theiler J, Gao F, Gupta R, Lapedes A, Hahn BH, Wolinsky S, Bhattacharya T: Timing the ancestor of the HIV-1 pandemic strains. Science 2000;288:1789–1796.

2 Neel C, Etienne L, Li Y, Takehisa J, Rudicell RS, Bass IN, Moudindo J, Mebenga A, Esteban A, van Heuerswyn F, Liegeois F, Kranzusch PJ, Walsh PD, Sanz CM, Morgan DB, Ndjango JBN, Plantier JC, Locatelli S, Gonder MK, Leendertz FH, Boesch C, Todd A, Delaporte E, Mpoudi-Ngole E, Hahn BH, Peeters M: Molecular epidemiology of simian immunodeficiency virus infection in wild-living gorillas. J Virol 2010;84:1464–1476.

3 Etienne L, Nerrienet E, LeBreton M, Bibila GT, Foupouapouognigni Y, Rousset D, Nana A, Djoko CF, Tamoufe U, Aghokeng AF, Mpoudi-Ngole E, Delaporte E, Peeters M, Wolfe ND, Ayouba A: Characterization of a new simian immunodeficiency virus strain in a naturally infected *Pan troglodytes troglodytes* chimpanzee with AIDS related symptoms. Retrovirology 2011;8:4.

4 Brennan CA, Bodelle P, Coffey R, Devare SG, Golden A, Hackett J, Harris B, Holzmayer V, Luk KC, Schochetman G, Swanson P, Yamaguchi J, Vallari A, Ndembi N, Ngansop C, Makamche F, Mbanya D, Gürtler LG, Zekeng L, Kaptue L: The prevalence of diverse HIV-1 strains was stable in Cameroonian blood donors from 1996 to 2004. J Acquir Immune Defic Syndr 2008;49:432–439.

5 UNAIDS/WHO. http://www.who.int/hiv/pub/epidemiology/pubfacts.

6 Fultz PN, McClure HM, Anderson DC, Swenson RB, Anand R, Srinivasan A: Isolation of a T-lymphotropic retrovirus from naturally infected sooty mangabey monkeys *(Cercocebus atys)*. Proc Natl Acad Sci USA 1986;83:5286–5290.

7 Lemey P, Pybus OG, Wang B, Saksena NK, Salemi M, Vandamme AM: Tracing the origin and history of the HIV-2 epidemic. Proc Natl Acad Sci USA 2003;100:6588–6592.

8 Burgard M, Jasseron C, Matheron S, Damond F, Hamrene K, Blanche S, Faye A, Rouzioux C, Warszawski J, Madelbrot L: Mother-to-child transmission of HIV-2 infection from 1986 to 2007 in the ARNS French Perinatal Cohort EPF-CO1. Clin Infect Dis 2010;51:833–843.

9 Tienen C, van der Loeff MS, Zaman SM, Vincent T, Sarge-Njie R, Peterson I, Leliqdowicz A, Jave A, Rowland-Jones S, Aaby P, Whittle H: Two distinct epidemics: the rise of HIV-1 and decline of HIV-2 infection between 1990 and 2007 in rural Guinea-Bissau. J Acquir Immune Defic Syndr 2010;53:640–647.

10 Gunthard HF, Huber M, Kuster H, Shah C, Schüppach J, Trkola A, Böni J: HIV-1 superinfection in an HIV-2-infected woman with subsequent control of HIV-1 plasma viremia. Clin Infect Dis 2009;48:e117–e120.

11 Iordanskiy S, Wattke M, Feng Y, Wood C: Subtype-associated differences in the HIV-1 reverse transcription affect the viral replication. Retrovirology 2010;7:85.

12 Pathak VK, Temin HW: Broad spectrum of in vivo forward mutations, hypermutations, and mutational hotspots in a retroviral shuttle vector after a single replication cycle: substitutions, frameshifts, and hypermutations. Proc Natl Acad Sci USA 1990;87:6019–6023.

13 Pathak VK, Temin HM: Broad spectrum of in vivo forward mutations, hypermutations, and mutational hotspots in a retroviral shuttle vector after a single replication cycle: deletions and deletions with insertions. Proc Natl Acad Sci USA 1990;87:6024–6028.

14 Alvarez M, Matamoros T, Menendez-Arias L: Increased thermostability and fidelity of DNA synthesis of wild-type and mutant HIV-1 group O reverse transcriptases. J Mol Biol 2009;392:872–884.

15 Shimizu N, Okamoto T. Moriyama EN, Takeuchi Y, Gojobori T, Hoshino H: Patterns of nucleotide substitutions and implications for the immunological diversity of human immunodeficiency virus. FEBS Lett 1989;250:591–595.

16 Kijak GH, Simon V, Balfe P, Vanderhoeven J, Pampuro SE, Zala C, Ochoa C, Cahn P, Markowitz M, Salomom H: Origin of human immunodeficiency virus type 1 quasispecies emerging after antiretroviral treatment interruption in patients with therapeutic failure. J Virol 2002;76:7000–7009.

17 Buzon MJ, Wrin T, Codoner FM, Dalmau J, Phung P, Bonjoch A, Coakley E, Clotet B, Martinez-Picado J: Combined antiretroviral therapy and immune pressure lead to in vivo HIV-1 recombination with ancestral viral genomes. J Acquir Immune Defic Syndr 2011;57:109–117.

18 Zhu T, Muthui D, Holte S, Nickle D, Feng F, Brodie S, Hwangbo Y, Mullins JI, Corey L: Evidence for human immunodeficiency virus type 1 replication in vivo in CD14+ monocytes and its potential role as a source of virus in patients on highly active antiretroviral therapy. J Virol 2002;76:707–716.

19 Duarte EA, Novella IS, Weaver SC, Domingo E, Wain-Hobson S, Clarke DK, Moya A, Elena SF, de la Torre JC, Holland JJ: RNA virus quasispecies: significance for viral disease and epidemiology. Infect Agents Dis 1994;3:201–214.

20 Law M, Murayama T, Lewis J, Giang E, Tarr AW, Stamataki Z, Gastaminza P, Chisari FV, Jones IM, Fox RI, Ball JK, McKeating JA, Kneteman NM, Burton DR: Broadly neutralizing antibodies protect against hepatitis C virus quasispecies challenge. Nat Med 2008; 14:25–27.
21 Onafuwa-Nuga A, Telesnitzky A: The remarkable frequency of human immunodeficiency virus type 1 genetic recombination. Microbiol Mol Biol Rev 2009;73:451–480.
22 Simon-Loriere E, Martin DP, Weeks KM, Negroni M: RNA structures facilitate recombination-mediated gene swapping in HIV-1. J Virol 2010;84:12675–12682.
23 Fang G, Weiser B, Kuiken C, Philpott SM, Rowland-Jones S, Plummer F, Kimani J, Shi B, Kaul R, Bwayo J, Anzala O, Burger H: Recombination following superinfection by HIV-1. AIDS 2004;18:153–159.
24 Kuiken C, Leitner T, Foley B, Hahn B, Marx P, McCutchan F, Wolinsky S, Korber B (eds): HIV Sequence Compendium. Los Alamos National Laboratory, Los Alamos, 2009http://www.hiv.lanl.gov/.
25 Motomura K, Chen J, Hu WS: Genetic recombination between human immunodeficiency virus type 1 (HIV-1) and HIV-2, two distinct human lentiviruses. J Virol 2008;82: 1923–1933.
26 Domingo E: Mechanism of viral emergence. Vet Res 2010;41:38–52.
27 Dai L, Stevenson M: A novel motif in HIV-1 Nef that regulates MIP-1beta chemokine release in macrophages. J Virol 2010;84:8327–8331.
28 Bocharov G, Ford NJ, Edwards J, Breinig T, Wain-Hobson S, Meyerhans A: A genetic-algorithm approach to simulating human immunodeficiency virus evolution reveals the strong impact of multiple infected cells and recombination. J Gen Virol 2005;86: 3109–3118.
29 Van der Kuyl AC, Kozacynska K, van den Burg R, Zorgdrager F, Back N, Juriaans S, Berkhout B, Reiss P, Cornelissen M: Triple HIV-1 infection. N Engl J Med 2005;352: 2557–2559.
30 Batmanian J, Brew BJ: Clinical significance of central nervous system as sanctuary site for HIV. J HIV Ther 2005;10:16–21.
31 Dahl V, Josefsson L, Palmer S: HIV reservoirs, latency and reactivation: prospects for eradication. Antiviral Res 2010;85:286–294.
32 Smith DM, Wong JK, Hightower GK, Ignacio C, Koelsch KK, Petropoulos CJ, Richman DD, Little SJ: HIV drug resistance acquired through superinfection. AIDS 2005;19: 1251–1256.
33 Rachinger A, Stolte IG, van de Ven TD, Burger JA, Prins M, Suitemaker H, van' t Wout AB: Absence of HIV-1 superinfection 1 year after infection between 1985 and 1997 coincides with a reduction in sexual risk behaviour in the seroincident Amsterdam Cohort of homosexual men. Clin Infect Dis 2010;50: 1309–1315.
34 Lorenzo-Redondo R, Borderia AV, Lopez-Galindez C: Dynamics of in vitro fitness recovery of HIV-1. J Virol 2011;85:1384–1390.
35 Henriet S, Mercenne G, Bernacchi S, Paillart JC, Marquet R: Tumultous relationship between the human immunodeficiency virus type 1 viral infectivity factor (Vif) and the human APOBEC-3G and APOBEC-3F restriction factors. Microbiol Mol Biol Rev 2009;73:211–232.
36 Van der Vlist M, Geijtenbeek TB: Langerin functions as an antiviral receptor on Langerhans cells. Immunol Cell Biol 2010;88:410–415.
37 Sauter D, Specht A, Kirchhoff F: Tetherin. Holding on and letting go. Cell 2010;141: 392–398.
38 Sterjovski J, Churchill MJ, Roche M, Ellett A, Farrugia W, Wesselingh SL, Cunnigham AL, Ramsland PA, Gorry PR: CD4-binding site alterations in CCR5-using HIV-1 envelopes influencing gp120-CD4 interactions and fusogenicity. Virology 2011;410:418–428.
39 Swenson LC, Mo T, Dong WW, Zhong X, Woods CK, Jensen MA, Thielen A, Chapman D, Lewis M, James I, Heera J, Valdez H, Harrigan PR: Deep sequencing to infer HIV-1 co-receptor usage: application to three clinical trials of maraviroc in treatment-experienced patients. J Infect Dis 2011;203:237–245.
40 Julg B, Moodley ES, Oi Y, Ramduth D, Reddy S, Mncube Z, Gao X, Goulder PJ, Detels R, Ndungu T, Walker BD, Carrington M: Possession of HLA class II DRB1*1303 associates with reduced viral loads in chronic HIV-1 clade C and B infection. J Infect Dis 2011;203: 803–809.
41 Troyer JL, Nelson GW, Lautenberger JA, Chinn L, McIntosh C, Johnson RC, Sezgin E, Kessing B, Malasky M, Hendrickson SL, Li G, Pontius J, Tang M, An P, Winkler CA, Limou S, Le Clerc S, Delaneau O, Zagury JF, Schuitemaker H, Van Manen D, Bream JH, Gomperts ED, Buchbinder S, Goedert JJ, Kirk GD, O'Brien SJ: Genome-wide association study implicates PARD3B-based AIDS restriction. J Infect Dis 2011;203:1491–1502.