International Journal of Molecular Medicine and Advance Sciences 1 (4): 351-356, 2005

HIV-1/ Host Cell Interactions as Genomic Instability of Both HIV-1 and Host Cell

Lawrence M Agius
Department of Pathology, St Luke's Hospital, Gwardamangia,
Medical School University of Malta, Pieta, Malta, Europe

Abstract: HIV-1 infection would initially predispose to neoplastic transformation in terms of a progressive lymphocytic proliferation followed by the onset of an immunodeficiency state. Both virion genomic integration and also active host cell proliferation would perhaps participate in the establishment of an often multifocal Primary CNS Lymphoma of AIDS type. Repeated opportunistic infections in AIDS patients tend to especially involve the central nervous system to also carry an increased risk of neoplastic transformation of the reactive B lymphocytes reaching the brain. A microenvironmental set of circumstances in patients with AIDS would predispose to nonHodgkin's lymphoma largely in terms of an HIV-1 infection that progresses concurrently with evolving cell replication, immunodeficiency and repeated opportunistic infections as caused by several different potential pathogens. Epstein-Barr virus infection in particular appears closely related to Hodgkin's disease that develops in some AIDS patients. A viral role in the development of lymphomas and of Kaposi sarcoma in HIV-infected individuals would account for neoplastic aggressiveness and for a particular predilection for Primary CNS lymphoma. Such a role perhaps implicates viral integration within the genome of host cells that are actively proliferating or else infected by multiple viral pathogens such as EBV, HIV-1, CMV and herpes virus.

Key words: HIV-1, cell interactions, genomic instability, host cell

INTRODUCTION

MULTIPLE DIFFERENT CYCLES OF VIRAL INFECTION BEYOND DIMENSIONS OF JUST VIRAL REPLICATIVE ACTIVITY

Systems of evolution of viral infection might arise and progress as constitutive functions of a full series of different but integral cyclical activities involving virus participation in cellular and tissue homeostasis. In this essential sense of a dimensional involvement of various separate and distinctive pathways of interactive effect, various forms of relative interplay between viral particle activity and cellular homeostatic activities would help redefine a generic pathway of integrative and constitutively evolving viral infection. This appears particularly significant since a subgroup of long-term nonprogressors of HIV-1 infection occurs, characterized by low HIV-1 replication rate and low viral load[1].

In terms that would indicate a pathobiologic series of disturbances arising from homeostatic loss of control of cellular activities as viral evolution and especially as evolving viral-host cell relationships, various systems would appear to progress essentially as a viral infection beyond simple viral replicative activity. This would appear particularly significant in terms of frequent discordance in the level of multiple HIV-1 populations in different compartments of the body[2] of an infected individual.

It is in this sense perhaps that one would speak of an activity arising as a viral infectious type evolving in terms simply of cyclical activities. Different and inter-related generic cyclical-type pathways would largely characterize the viral infection. Viral infection might be specifically defined as an inbuilt series of interactive cycles within others, promoting further progression and evolution in terms of utilization and of disturbance of cellular homeostasis that is distinct from just replication of virus or of simply cellular injury.

Manipulative systems of host cell-virus interaction would perhaps account for cyclical interactions leading to further progressive interactivity and complexity in any viral infectious state. Microsatellite alterations, as an index of widespread genomic instability, frequently develops in HIV-associated cervical intraepithelial neoplasia and this may very well play a crucial role in the development of HIV-associated neoplasia[3]. The ellipse phase with absorption, penetration and uncoating of the virion would progress to synthesis and to a viral multiplication cycle. Progressing early and late periods of viral infection would promote effective release of virus as an evolving series of interactions specifically related to potential cellular injury and also to different generated host cell-virus relationships.

In such a context, also, poor adherence to an antiretroviral therapy program would especially tend to promote emergence of resistant HIV-1 variants[5].

Corresponding Author: Lawrence M Agius, 14, Guzeppi Caruana Str., Tal-virtu, Rabat, Rbt09 Malta, Europe
Tel: 356 21451752, 356 2595 1663 Fax: 365 21114286

THE ACTIVE HIV-1 INFECTION IS ESSENTIALLY DISTINCT FROM JUST VIRAL REPLICATIVE STATUS

In terms specifically of an active viral infection that would progress beyond considerations simply of essential viral replication, one might view HIV-1 infections as essentially various forms of adaptation towards non-replicative involvement of cells by the retrovirus. Indeed, besides a dynamically evolving system of transcription of integrated HIV-1 provirus in the host genome, there would develop an HIV-1 infection as the creation of essential genetic variants of the virus that arise from characterized interchange between episomal and proviral cyclical expressions of the virion. Hypermutation of viral DNA and instability of the genome would specifically arise as host cell participation as exemplified by CEM 15 (apolipoprotein B in RNA editing enzyme)[5].

It is perhaps in this sense especially tat retroviral chemotherapy in AIDS patients so often results in the emergence of resistant HIV-1 strains, in the added evolving context of progression of the patient's AIDS status.

It is indeed in view of essential evolutionary patterns of HIV-1 instability in response to a full range of potentially selective pressures that AIDS would constitute a composite phenomenon. An active replicative state of the virion would determine specific dynamics of the infected HIV-1 state related to both target cell depletion and also to decreased infectivity of unstable HIV-1 genomes[6].

LATENT INACTIVE OR NONREPLICATIVE HIV STATES IN HOST CELLS POTENTIALLY PROMOTED VIA HIV-1 TRANSCRIPTION/TRANSLATION CONTROL?

Genetic instability, as evidenced by replicating HIV-1[5] might in various ways relate particularly to enhancing and promoting systems for replication of the HIV integrated provirus. In this sense, for example, promoter regions upstream from the start point, and also enhancement in the form of response elements would potentially constitute mechanisms whereby Nuclear Factor kappa beta or Interleukin 6 would influence transition of latent to active forms of HIV infection of the cell. Also, with HIV infection IgM VH gene repertoires become progressively more unstable with abnormal expression and fluctuations in expression levels of VH 3 genes in particular[7].

In this regard, perhaps, subsidiary pathways of influence would operate within an equilibration series of changes that are translated as progeny HIV particles, on the one hand, and also as an overall system of integration of latent HIV provirus, on the other. Vpr, an accessory gene of HIV appears to induce chromosomal breaks that promote gene amplification and a subsequent bridge-breakage-fusion cycle leading to genomic instability.

Within such an operative framework, perhaps, chromatin unfolding user sites of promoter regions or of inducer response elements or else differential mRNA splicing or even differential polyadenylation capping of the 3' end of the mRNA molecule would inter-relate as systems of control of viral protein synthesis. In this regard, conformational flexibility of internal loops might allow viral genomic dimerization and splicing and thus promote selective encapsidation of the intact genomic RNA of the HIV-1 virion against a background of innumerable cellular mRNAs[8].

HIV-1 RNA concentration would appear a significant form of assessing effects of anti-retroviral therapy especially in terms of actual HIV-1 antigen testing as for p24[9].

In terms therefore of a single overall pathway of regulated transcription of the provirus and of reported translation of viral mRNA molecules, not only might the amount of viral protein produced be regulated tightly, but the actual interchange of integrated provirus with episomal virus might be strategically influenced in terms particularly of latent inactive or nonreplicative systems of HIV cellular involvement.

CONTRASTING SYSTEMS OF LYMPHOCYTE SUBSET DEPLETION, VERSUS LYMPHOMAGENESIS IN HIV-1 INFECTION AS DIRECTLY CONTROLLED ALSO BY CONSTITUTIONAL HOST CELL TRANSCRIPTION FACTORS

A system of latency, as exhibited by the subfamily Lentiviridae, would constitute perhaps forms of controlled expression of various viral proteins such as those constituting the intact HIV-1 particle. It is in such terms, indeed, that an interplay of conversion forms of HIV-1 origin would contribute to a strictly inter-related system of controlled expression of the virus in a manner promoting the creation of persistently latent HIV infection.

It is significant also that the elimination of inhibitory or instability elements within unspliced and partially spliced messenger RNAs is sufficient for efficient expression of HIV-1 mRNAs in the absence of Rev or other post-transcriptional activation[10].

The actual opportunities for activation of such latent infectious forms of HIV-1 might specifically relate to host cell transcriptional factors, especially those that would directly flank as 4-6 base repeat fragments on either side of the integrated HIV-1 provirus. Furthermore, along such lines, it would be relevant perhaps to consider host cell constitutional factors as arising from promoters and enhancers of genomic transcription as simply direct

determinants of activation of latently integrated HIV provirus. Vaccines of live attenuated HIV virus may revert to virulence via mechanisms or recombine to endogenous retroviral sequences. Multiplication of remaining sequence motifs appears to account for emergence of rapidly replicating virus in deleted HIV-1 vaccine strains[11].

Such constitutional transcriptional control by the host cell would perhaps constitute a mechanism of evolutionary change in terms of an HIV-1 particle that responds to various selective pressures influencing directly not only latency and activation of virion production, but also a full series of pathways ranging from lymphocyte subtype depletion to lymphomagenesis. In this regard, decreased expression of the CC chemokine receptor (CCR5) increases resistance to HIV-1 infection[12].

In effective terms, one might perhaps equate activation of HIV-1 particles with systems either focused primarily on progeny virus production or else on an essential malignant transformation as determined at least in part by actual constitutional attributes of that individual host cell infected by the HIV-1 virions.

Evolutionary interplay between episomal and provirus HIV-1 particles in an AIDS patient might arise particularly in a context of the considerably complex attributes of the HIV-1 genome. HIV-1 integrase, when unstable, would potentially modify forms of insertion of the viral genome relative to maintenance and integrity of the host cell genome[13].

Such genomic complexity would involve particularly transcription of gag-pro-pol precursor in addition to at least six additional genes that regulate expression of the HIV genome itself. Multiple spliced messenger RNAs are involved in subsequent protein translation and include tat (trans-activator) protein. Tat protein binds to the trans-activation response element between plus 19 and plus 42 positions in the viral RNA and functions to increase about 100 fold the number of complete HIV transcripts produced. Multiple inhibitory/instability elements within mRNAs that encode structural HIV-1 proteins decrease efficiency of viral protein expression[14].

Rev protein[17] is involved in preventing splicing whereas early during HIV transcription there are multiple spliced messengers encoding for tat, rev, and other regulatory proteins; later, the increased Rev provides messenger RNA splices encoding structural HIV proteins. Unspliced or partially spliced messenger RNAs are transported from the nucleus bound to Rev at the Rev response element. Indeed, mutant heterogeneous nuclear ribonucleoprotein A1 appears to contribute to gene instability in terms of complementation of Rev activity[18].

A DIRECTLY CONTRASTING STATE OF INTEGRATED DEPLETIVE AND EXCESSIVE TYPE IN THE AIDS PATIENT OF AN IMMUNODEFICIENT AND NEOPLASTIC CHARACTER

A directly operative system of greatly amplified production of transcribed RNA would appear to actively transform cells to a state of induced overactivity as related particularly to cell division. Indeed, Vpr induces abnormal cell cycling with accumulation of cells at the G2-M transition phase[19] as an abnormal checkpoint control of mitotic division[20].

In such terms, perhaps, one might actually refer to mechanistic pathways of induced transformation as directly leading to a malignant state of cellular activity that arises and progresses strictly as a system of inbuilt-positive control.

The basic mechanisms proposed for oncogene activation in terms of a translation event, or particularly, in terms of recombinant creation at often multiple points in the cell genome, would perhaps have to be dimensioned with reference to a strictly single or integral mechanistic pathway of transformational events that paradoxically are both amplified and evolving.

Amplification of incorporated oligonucleotide repeats is a major cause of genomic instability. Repeated DNA synthesis induced by HIV-1 reverse transcriptase would tend to develop due to abnormal copying of polymerases[21].

It is indeed in terms of such an evolving amplification phenomenon as related specifically to transcribed RNA production that crucial aspects of the role or roles of retrovirus such as HIV-1 in the generation and subsequent greatly amplified progression of various forms of malignancy would contribute towards possibly amplified neoplastic progression. It appears significant also that flexibility and internal motions of HIV-1 reverse transcriptase are centrally involved in the biology of HIV infection[16].

It is perhaps with reference to a progressively amplifying series of pathways that technically constitute progressiveness of the AIDS state that one might better understand how an induced immunodeficient state largely through its severe degree of progressiveness would inherently constitute an integral series of mechanistic pathways promoting inevitably lymphomagenesis.

Also, centromeric instability as possibly induced through hypomethylation may help explain development of HIV-1 associated nonHodgkin's lymphoma particularly with its progression[21]. Indeed, perhaps Kaposi sarcoma would evolve as a generated system of participation in such a progressive series of amplification steps that would strictly correlate with events of integration of HIV provirus relative to lymphocyte depletion.

Such a complex series of interacting pathways in the evolving AIDS state of the patient concerned might really constitute a basis for dynamic change that would be definable as generated and transformed genotype and phenotype interactions.

Even with regard to actual forms of integration of the HIV-1 genome within host cell DNA, cellular participation appears a potentially significant contributor as related for example to integrase activity[22].

It is with reference, on the one hand, of various forms of injury to the cell genome, concurrent and also subsequent to integration of the HIV provirus and on the other hand with a series of basic forms of disturbance between such genotype injury and phenotype determination that amplification in malignant transformation would constitute a quantitative determination in qualitative terms.

Malignancy, generated as pathobiologic progressiveness in AIDS patients would simply involve different forms of how quantitative depletion of lymphocytes would provoke also an associated quantitative phenomenon of endless amplification. This process would strictly evolve as systems of paradoxically contrasting pathways of a depletive and excessive nature in any one individual patient suffering from HIV infection of AIDS type.

Also, with regard to vertical transmission of HIV-1 from mother to infant, Caesarian section does not necessarily induce increases in viral load relative to a postoperative increase in the CD4T lymphocyte count[23].

EPISOMAL AND PROVIRAL INTERACTIONS OF HIV-1 PARTICLES AS DETERMINED BY THE INFECTED HOST CELL ALONG VIRAL GENOMIC EVOLUTIONARY PATHWAYS IN A GIVEN AIDS PATIENT

Acquisition of viral attributes as evidenced by the outbreak of various viral epidemics and pandemics might effectively relate not simply to transforming qualities for a previously endemically occurring viral strain but more specifically to the attainment of new dynamic equilibria between episomal and integrated viral particles within infected cells. Microsatellite alterations in particular reflect widespread genomic instability in HIV-associated malignancies including lung carcinomas[24].

In terms of the HIV-1 particle the AIDS epidemic would constitute perhaps alternate resolutions of such episomal and provirus equilibria relative to an overall concept of viral "evolution". Certainly, strictly selective pressures on various advantagenous attributes with the emergence of a dominant viral strain would have to be considered within a context of variable degrees of effective stability of the viral genome. Indeed, the high degree of genetic instability shown by various HIV particle clones even in one give AIDS patient would somehow have to be reconciled with an overall phenomenon inherent to the primary outbreak of the AIDS epidemic in the late 1970s and early 1980s and more significantly with also the appearance of progressive widespread AIDS epidemics in Africa, Europe, Asia and United States.

It is probably because of viral evolving patterns of recombination, genetically, that one would perhaps better understand predominant host cell determination systems that paradoxically characterize the genetic HIV particle instability relative to the overall preset catalogue of retroviral patterns of episomal and proviral involvement of that cell.

Indeed, one might perhaps envisage HIV-1 infection simply as a system of determined patterns that are pre-set by host cells in a manner specifically permissive for a persistent phase of viral infection. Indeed, neoplastic transformation of such host cells would constitute such duality of interacting systems whereby host cell mechanisms in various ways allow integration of HIV provirus within the cell genome. Such integration would specifically allow or even promote the subsequent emergence of genetic variants of the original HIV infecting particle. In this sense, the essential conceptual framework of a viral evolutionary pathway for HIV-1 would inherently implicate dynamics of the HIV infection in any given individual AIDS patient that would subsequently be conducive to neoplastic transformation[25].

Furthermore, the contrasting sets of immunodeficiency and of lymphocyte depletion on the one hand and of neoplastic transformation particularly of lymphocytes as classically seen in AIDS patients on the other would effectively and directly reflect an integrally evolving viral particle that owes its evolving genetic instability to attributes primarily arising from relative interactions between episomal and proviral HIV-1 particles, as determined especially by host cell attributes.

IS HIV-1 INFECTION SIMPLY EPISOMAL INVOLVEMENT THAT PROVIDES INTEGRATIVE CREATION OF DIFFERENT PROVIRAL MODES OF PERSISTENT PROGRESSION IN AIDS

The high degree of genetic instability demonstrated by HIV-1 virions would perhaps constitute an effective basis for the establishment of a persistent infectious state that depends on the creation of attributes of Defective Interfering Virus Particles. It is in such terms, of a

conceptual series of mechanistic effects arising on the one hand from interference of normal pathways of wild virus replication and on the other from various modifications of viral genomic and antigenic (or molecular) attributes as an escape phenomenon from cellular control that one might recognized Defective Interfering Virus Particles in evolved forms of persistently progressive infection.

Indeed, perhaps, it is in terms strictly arising from deletions of the viral genome that one would in various ways better understand evolutionary progression and transformation of pathobiologic attributes of virus or of viral strains arising from and inducing phenomena ranging from immune deficiency to neoplastic transformation[26] within a single integral context of replicative episodes of different opportunistic infections in any given AIDS patient.

Defective interfering virus particles might actually be envisaged as simply a potentiality for multivariant adaptive change that in various ways would actively and also passively permit and promote evolving pathways of complementation and cooperation between different virus types leading to a single overall system of a progressively infective state, as evidenced classically by the AIDS epidemic. The actual identity of such a process of integrative effects in terms of an HIV infection that is paradoxically both progressive and yet persistent for a number of years would appear suggestive of a correlative series of complementary mechanisms between different genetic variants of the HIV virus arising particularly through viral multiplication in that individual AIDS patient concerned.

The creation of a full series of gene products that is required for HIV particle replication might relate particularly to concurrent processes involving template switching between homologous or heterogeneous strands of DNA or RNA that would tend to characterize aspects of integration of the HIV provirus itself.

In terms therefore of both intragenic and extragenic presence of deletion, and also of exchange of genetic material, an essentially persistent state of progressive infection by the HIV virus would in addition also constitute dynamic interchange between integrated provirus and intact infectious viral particles through such systems as episomal stages of the HIV infection. Indeed, episomal HIV particles within cells would perhaps constitute different mechanistic opportunities for HIV to both integrate within the cell genome, and also to promote progressive variant creation of HIV within one overall system of genetic instability of such HIV particles.

CONCLUSION

Multiple genomic variants of infecting HIV define episomal/proviral cycling and integrative HIV-host cell genomic instability in AIDS patients.

Active participation of a whole series of events may both interact and also promote the potentialities of evolving HIV infection in terms related directly to the progressive instability of the HIV genome. In terms of any given AIDS patient that might progress more significantly with reference to multiple genomic variants of the infecting HIV virion, one would in addition recognize a potentiality for episomal cycling and proviral integration as a dual system in such participating roles of evolving HIV genomic instability. One would indeed perhaps associate an essential progressiveness in HIV infection not simply in terms of an increase in the HIV load but particularly in terms of different evolving modes of integration of the HIV within the host cell genome. In this sense, one would perhaps associate certain cycling attributes of episomal retrovirus to essential replicative and also nonreplicative events determining forms of potential change as reflected in subsequent emergence of genomic variants of the HIV virion. Indeed, in terms that would perhaps better define HIV infection as a host cell participating series of roles in the active creation of a whole group of evolving and emerging genomic variants of the HIV virion, one would view actual replicative or multiplication cycles of the retrovirus as simply a consequence and not a pathogenesis in the active HIV-host cell infection process.

One would perhaps recognize full cycles of influence in terms of participating interaction between episomal and proviral systems that would relate not primarily to subsequent establishment of viral replication cycles but to the essential creation of various forms of dimensional integration in the host genome.

Even in terms of redefinition of the primary infectious state of the host cell by the HIV virion, one might in addition perhaps view multiple different genomic variants of the HIV that would tend to infect any given host cell in AIDS in the added evolving context of genomic instability of both the HIV and the host cell infected.

REFERENCES

1. Wang, C.Y., J.L. Snow and W.P. Su, 1995. Lymphoma associated with human immunodeficiency virus infection. Mayo Clin. Proc., 70: 665-672.
2. Greatorex, J., J. Gallego, G. Varani and A. Lever, 2002.Structure and stability of wild-type and mutant RNA internal loops from the SL-1 domains of the HIV-1 packaging signal. J. Mol. Biol., 322:543-557.
3. Najera, I., M. Krieg and J. Karn, 1999. Synergistic stimulation of HIV-1 rev-dependent export of unspliced mRNA to the cytoplasm by hnRNP A1. J. Mol. Biol., 285: 1951-1964.

4. Mulder, L.C. and M.A. Muesing, 2000. Degradation of HIV-1 integrase by the N-end rule pathway. J. Biol. Chem., 275: 29749-29753.
5. Afonina, E., M. Neumann and G.N. Pavlakis, 1997. Preferential binding of Poly(A)-binding protein-1 to an inhibitory RNA element in the human immunodeficiency virus type 1 gag mRNA. J. Biol. Chem., 272:2307-2311.
6. Avidan, M.S., P. Groves, M. Blott and J. Welch *et al*., 2002. Low complication rate associated with Cesarean section under spinal anesthesia for HIV-1 infected women on antiretroviral therapy. Anesthesiology, 97:320-324.
7. Shimura, M., Y. Onozuka, T. Yamaguchi, K. Hatake, F. Takaku and Y. Ishizaka, 1999. Micronuclei formation with chromosome breaks and gene amplification caused by Vpr, an accessory gene of human immunodeficiency virus. Cancer Res., 59: 2259-2264.
8. Berkhout, B., K. Verholf, van J.L. Wamel, N.K. Bark, 1999. Genetic instability of live, attenuated human immunodeficiency virus type 1 vaccine strains. J. Virol., 73:1138-1145.
9. Bessudo, A., L. Rassenti, D. Havlir, D. Richman, E. Fergel and T.J. Kipps, 1998. Aberrant and unstable expression of immunoglobulin genes in persons infected with human immunodeficiency virus. Blood, 92: 1317-1323.
10. Tamasauskas, D., V. Powell, K. Saksela and K. Yazdanbakhsh, 2001. A homologous naturally occurring mutation in Duffy and CCR5 leading to reduced receptor expression. Blood, 97: 3651-3654.
11. Schneider, R., M. Campbell, G. Nasioulas, B.K. Felber and G.N. Pavlakis, 1997. Inactivation of the human immunodeficiency virus type 1 inhibitory elements allows Rev-independent expression of Gag and Gag/protease and particle formation. J. Virol., 71: 4892-4903.
12. Esnouf, R.M., J. Ren, E.F. Garman and D.O. Somers *et al*., 1998. Continuous and discontinuous changes in the unit cell of HIV-1 reverse transcriptase crystals on dehydration. Acta Crystallogr D. Biol. Crystallogr, 54: 938-953.
13. Martinez, J., D. Bell, R. Camacho and L.M. Henry-Reid *et al*., 2000. Adherence to antiviral drug regimens in HIV-infected adolescent patients engaged in care in a comprehensive adolescent and young adult clinic. J. Natl. Med. Assoc., 92: 55-61.
14. Vesanen, M., C.E. Stevens, P.E. Taylor, P. Rubinstein and K. Saksela, 1996. Stability in controlling viral replication identifies longterm nonprogressors as a distinct subgroup among human immunodeficiency virus type 1-infected persons. J. Virol., 70: 9035-9040.
15. Warschaw, K.E., J.N. Eble, A.F. Hood, S.E. Wolverteon and K.C. Halling, 1997. The Muir-Torre syndrome in a black patient with AIDS: histopathology and molecular genetic studies. J. Cutan. Pathol., 24: 511-518.
16. Schupbach, J., 2002. Measurement of HIV-1 p24 antigen by signal-amplification-boosted ELISA of heat-denatured plasma is a simple and inexpensive alternative to tests for viral RNA. AIDS Rev., 4: 83-92.
17. Wistuba, II., S. Syed, C. Behrens and M. Duog *et al*., 1999. Comparison of molecular changes in cervical intraepithelial neoplasia in HIV-positive and HIV-indeterminate subjects. Gynecol. Oncol., 74: 519-526.
18. Sawyer, J.R., C.M. Swanson, M.A. Koller, P.E. North and S.W. Ross, 1995. Centromeric instability of chromosome 1 resulting in multibranched chromosomes, telomeric fusions, and 'jumping translocations' of 1q in a human immunodeficiency virus-related non-Hodgkin's lymphoma. Cancer, 76: 1238-1244.
19. Ping, L.H., M.S. Cohen, I. Hoffman, P. Vernazza *et al*., 2000. Effects of genital tract inflammation on human immunodeficiency virus type 1 V3 populations in blood and semen. J. Virol., 74: 8946-8952.
20. Ricchetti, M. and H. Buc, 1996. A reiterative mode of DNA synthesis adopted by HIV-1 reverse transcriptase after a misincorporation. Biochemistry, 35: 14970-14983.
21. Wistuba, II., C. Behrens, S. Milchgrub and A.K. Virmani *et al*., 1998. Comparison of molecular changes in lung cancers in HIV-positive and HIV-indeterminate subjects. JAMA, 279: 1554-1559.
22. Mikaelian, I., M.J. Krieg, Gait and J. Karu, 1996. Interactions of INS (CRS) elements and the splicing machinery regulate the production of Rev-responsive RNAs. J. Mol. Biol., 257: 246-264.
23. Cherepano, V.P., W. Pluymers, A. Claeys, P. Proost, E. DeClercq and Z. Debyser, 2000. High level expression of active HIV-1 integrase from a synthetic gene in human cells. FASEB J., 14:1389-1399
24. Shimura, M., Y. Tanaka, S. Nakamura and Y. Minemoto *et al*., 1999. Micronuclei formation and aneuploidy induced by Vpr, an accessory gene of human immunodeficiency virus type 1. FASEB. J., 13: 621-637.
25. Zhang, H., H. Yang, R.J. Powerantz, C. Zhang, S.C. Arunachalam and L. Gao, 2003. The cytidine deaminase CEM 15 induces hypermutation in newly synthesized HIV-1 DNA. Nature, 424:94-98.
26. Strain, M.C., D.D. Richman, J.K. Wong and H. Levine, 2002. Spatiotemporal dynamics of HIV propagation. J. Theor. Biol., 18:85-96.