International Journal of Molecular Medicine and Advance Sciences 1 (2): 105-111, 2005

Proinflammatory HIV-1 Pathogenesis and Precarcinogenesis

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

Abstract: HIV-1 infection assumes the features of a systemic process affecting cellular cycling events and of inflammatory and neoplastic amplification. It would indeed appear that HIV-1 induces pathways of progression that are specifically transforming in terms of such amplification and self-amplification of cellular and microenvironmental events. The central nervous system in particular would constitute a manifestation of organ integrity that expresses the consequences of amplified transformation of pathobiologic lesions. Neoplasia of the lymphoreticular system would represent a characterization of the nature of such events as further projected by the HIV-1 infection evolving as AIDS dementia and Primary Lymphoma of the CNS and as Progressive Multifocal Leukoencephalopathy or opportunistic infection in general.

Key words: HIV-I, precarcinogenesis, systemic process

INTRODUCTION

Activated microglia contribute to neuronal cell death: A ramified microglial phenotype that reacts for CD163 appears to induce an inflammatory response to viral infection[1]. HIV encephalitis would account for how various phagocytic cells somehow become activated, concurrent with indirect virally-induced neuronal injury. Microglial activation would comprise different response patterns to neuronal injury that contribute to cell death.

Hiv-1 involves direct neurotoxic injury: HIV-1 env protein gp120 appears to be extremely toxic to neurons in the presence of evolving inflammation in the brain and spinal cord[2]. It activates a caspase-dependent apoptotic pathway, especially caspase-3[3] and reduces brain-derived neurotrophic levels in neuronal processes[4]. Such a process would appear linked to dynamics of neuronally induced cellular injury during this time.

It would perhaps be valid to consider dynamics of HIV entry within cells as a specific mechanism implicating facilitation by the accompanying inflammation in HIV encephalitis, especially in the presence of oxidative stress and opioids[5].

A process of tropism of HIV-1 involving macrophages and microglia of entry into neurons would precipitate neuronal cell injury. Neuronal injury might affect entry-related mechanisms culminating not only in DNA damage but also further reactive cellular changes and apoptosis. Intra-CNS viral burden may correlate with both the severity of neurologic disease and the generation of neurotoxic metabolites in HIV infection[6].

Facilitated hiv entry into cells in inflammation of HIV encephalitis states: A high degree of expression of CXCR4 chemokine receptors on hippocampal neurons in HIV encephalitis might involve events whereby inflammatory reactivity renders cells particularly susceptible to HIV entry[7,8].

In a fashion of inflammation-induced facilitation of neuronal infection by HIV, there would evolve a series of cascade events culminating in neuronal DNA damage and subacute neurodegeneration[9]. HIV-Tat suppresses Nerve Growth Factor-induced differentiation and promotes cellular proliferation by upregulating Id1 expression; this helix-loop-helix transcriptional factor influences neuronal survival and may be implicated in the pathogenesis of AIDS dementia [10].

In the setting of inflammation, HIV encephalitis would implicate HIV tropism for both macrophages and CD4+ T-lymphocytes.

Such a phenomenon would subsequently evoke inflammation-induced facilitation of HIV entry into cells as found in the CA4 sector of the hippocampus. Chemokines may induce neuronal cell death via microglial activation or directly through activation of chemokine receptors[10].

In the setting of inflammation, HIV encephalities would implicate HIV tropism for both marcophages CD4+ T-lymphocytes. Such a phenomenon would subsequently evoke inflammation induced facilitation of HIV entry into cells as found in the CA4 sector of hippocampus. Chemmokines may induced neurnal cell death via microglial activation or directly through activation of chemokinereceptors[11].

The accompanying gliosis and synaptic transport of HIV-1 Tat[12] would operatively induce an accompanying series of changes related to progressive loss of viability of associated neurons[13]. Astrocyte infection in HIV would induce rapid progression of dementia in some AIDS patients.

The HIV-1 protein Tat is secreted mainly by astrocytes, microglia and macrophages and taken up by neurons[14]. Occasional multinucleated giant cells noted in HIV encephalitis would correspond to an ongoing direct injury to cellular DNA subsequent to such facilitated HIV entry in the presence of ongoing inflammation. HIV-laden macrophages and CD4+ T lymphocyte infection would participate in persistent progression of neuronal injury linked to active inflammation in the neuronal microenvironment.

Cellular differential susceptibility to HIV gene sequence incorporation in the cell genome: The actual presence of HIV gene sequences in the cellular genome would specifically indicate ongoing susceptibility pathways related to progressive cell injury[15]. Markers of apoptosis such as nuclear DNA fragmentation and p53 immunoreactivity are more intensely expressed in HIV-1 infected individuals as compared to HIV-1 negative women[16].

One might recognize HIV gene sequences as potentiating influence in ongoing neuronal injury linked to various pathways of subsequent outcome in neuronal HIV infection.

Differential neuronal susceptibility would participate in ongoing HIV infection in a manner that specifically promotes latent incorporation of viral gene sequences in the absence of productive viral infection. HIV-1 regulatory protein transactivator of transcription protein (Tat) increases oxidative stress, ATP levels and mitochondrial membrane potential. Tat upregulates platelet activating factor. The increased mitochondrial membrane potential may promote Tat-induced neuronal apoptosis[6]. It is with regard to variable response on the part of latently infected neurons that there would evolve a spectrum of variability in inflammatory reactivity in relation to spatially distributed groups of neurons. One might perhaps recognize viral entry of susceptible neurons as evidence for a process of subsequent DNA damage linking viral entry mechanisms to evolving DNA patterns of cell injury.

Facilitated neurotoxic effect in hiv dementia with blood-brain barrier breakdown and inflammation: Toxic injury to brain microvascular endothelium would promote a series of subsequent events leading to a targeted release of cytokines and neurotoxins[17].

Such a phenomenon might comprise especially the release of inhibitory products of metabolism that accentuate production of neurotoxic substances. Inflammatory cytokines appear to constitute a facilitatory pathway in progression of events that either result in neuronal cell death or to white matter gliosis. Neuronal loss, altered dendritic arbor and decreased synaptic density are characteristic features in HIV-1 associated dementia[9].

Even in terms of breakdown of the blood-brain barrier, it would appear that various inflammatory mediators are injurious particularly in the presence of an endothelial cell layer that progressively both promotes hypoperfusion of smaller microvessels and hyperperfusion of larger microvessels. With such combined non-homeostatic hyperperfusion and hypoperfusion events, the blood-brain barrier dysfunction would culminate in an inflammatory response on the part of perivascular macrophages and brain resident microglia that augments response sensitivity to neurotoxins[18].

Virally induced injury to cellular dna in hiv encephalitis is inflammatory and integrative in nature: Nonspatial relationship of HIV-laden macrophages and neuronal DNA damage in HIV encephalitis would attest to a progression of neuronal cell death in this condition[19]. Inflammatory changes in the CNS might specifically evolve in terms of a neuronal apoptosis. Activation of cell surface receptors such as CXCR4 and the N-methyl-D-aspartate receptor may be triggered by HIV-1 proteins gp120 and Tat[20].

HIV-associated neurodegeneration might indicate modes of neuronal DNA damage relative to apoptotic cell death pathways, including the presence of p53 in neurons and microglia[21]. AIDS dementia would consequently develop in terms of modes of injury to neurons largely susceptible to apoptosis or to a unique neurodegeneration unrelated to inflammation-induced reactivity. Chemokine receptor activation, particularly CXCR4, may be associated with cell cycle alterations in HIV-1 induced neuroinflammation[22].

AIDS dementia would also tend to arise as a result of depletion of various trophic systems in conjunction with DNA injury as a consequence of HIV infection of individual neurons.

Dissociation from inflammatory cell changes would better account for progression in HIV encephalitis that evolves as direct virally induced injury to and integration in neuronal DNA.

Blood-brain barrier permeability and compartmentalization of HIV: Increased P-glycoprotein expression would reflect dynamics of blood-brain barrier permeability increasing or otherwise facilitating entry of

HIV into the CNS[23]. P-glycoprotein is a membrane-associated, energy-dependent, efflux transporter [24].

HIV infection would involve a cellular response on the part, particularly, of astrocytes in facilitating both compartmentalization and proliferation of HIV.

Reactive oxygen species induce injury to endothelial cells in conjunction with increased P-glycoprotein expression by astrocytes. Viral replication and viral compartmentalization may be linked to protease inhibitor access to the brain.

Increased blood-brain barrier permeability and HIV replication appear induced phenomena promoted by astrocytic expression of P-glycoprotein.

Compartmentalization of HIV is a phenomenon more directly linked to possible projected progression and replication of infectious HIV.

MORE PROFOUND GENOMIC INTEGRATIVE EFFECTS OF HIV INFECTION IN PATIENTS ON HAART THERAPY: Changing patterns of HIV neuropathology in the HAART era would correspond to dynamic transformation in direct consequence to the HIV infection itself[25]. It might be significant to consider persistent HIV infection an evolving consequence of HAART treatment in some cases of latent infection.

HIV production by infected neurons might prove a direct consequence of integration of the virus within the neuronal genome. Latent viral infection is significant, not only in possible subsequent reactivation of the viral infection, but also as a concurrently active consequence of HIV integration within cellular genomes of neurons, astrocytes, microglia, macrophages and lymphocytes.

Non-Hodgkin's lymphoma may represent one possible consequence of genomic integration of HIV.

The progression of HIV cognitive dysfunction in patients on HAART treatment for HIV encephalitis might reflect to a great extent the development of novel attributes of a viral infection that more directly compromises genomic function and physiology in a wide variety of cell types.

Activated perineuronal microglia mark an early stage in the subsequent incorporation of hiv within cellular genomes:

Macrophages and microglia appear to fundamentally protect nearby neurons in a manner inducing oxidative stress and glutamate production, on the one hand and in counteracting antioxidant and glutamate consumption, on the other[26]. Astrocytes appear implicated in HIV infection in a manner that promotes a rise in extracellular glutamate. Perineuronal microglia might constitute a clearing mechanism implicating in particular increased expression of excitatory amino acid transporters, perhaps as a function of early injury to adjacent neurons. AIDS dementia comprises an inter-related series of mechanistic pathways derived from such persistent activation of perineuronal microglia that eventually prove ineffective in controlling both HIV replication and incorporation within cellular genomes.

Dynamics of latent viral infection in progressive hiv infection with decreased levels of hiv-rna csf levels: Decreased HIV-RNA levels in the CSF in patients with HIV-encephalitis and concurrent Progressive Multifocal Leukoencephalopathy might develop in cases of evolving HIV-1 infection[27]. The possible resolution of HIV-1 as a consequence of evolving Progressive Multifocal Leukoencephalopathy due to JCV infection would implicate a latent inflammatory state with scanty lymphocytic infiltrates in the white matter.

The distinction of a leukoencephalopathy from leukoencephalitis in Progressive Multifocal Leukoencephalopathy would perhaps revolve around dynamics of a latent viral infection involving variably activated endogenous JCV previously acquired and residing in bone marrow stem cells, B lymphocytes and kidneys.

Resolved dynamics of latent viral infection would account for an HIV infected state that progresses in the face of decreased HIV-1 RNA levels in CSF.

Neuronal-astrocyte interactions compound neuronal cell death injury in hiv infection: A propensity for neuronal apoptosis might reside with astrocytic and microglial activation that progresses largely in terms of ongoing chemokine and cytokine reactivity to the HIV infected state[28]. It might be significant to consider how modes of interaction of neurons with astrocytes would be conducive to transformed HIV handling by neurons and even by macrophages and microglia.

An astrocytic participating role in evolving HIV infection of neurons would implicate apoptosis in the production of stromal-derived factor-1alpha.

This alpha chemokine appears produced by astrocytes and especially by neurons.

Interactivity between neurons and astrocytes in terms of cytokine and chemokine production might entail a variety of lesions that predetermine outcome of HIV-infected cells. The progressive course of cognitive decline in HAART treated patients with HIV encephalitis might specifically implicate activation of neurons and astrocytes that further participate in dynamics of delivery of HIV virions by macrophages and microglia.

Concurrent viral infections contribute to progression of HIV Infection: Active transport of Human Herpes Virus-6 into the CSF involves a hyperpermeability of the blood-

brain barrier in conjunction with dynamics of viral loading and active HIV-1 infection of endothelium and neurons[29]. Tat produced by HIV stimulates several-fold the replication of DNA initiated at the JCV origin; exogeneous Tat possibly influences JCV replication in oligodendrocytes[30].

It is significant that such blood-brain barrier hyperpermeability to Human Herpes Virus-6 entry into the CSF would allow progression particularly of opportunistic infections of the CNS such as cytomegalovirus infection.

It appears appropriate to consider how HIV-infection is a consequence of other possible, previously acquired, viral infections in the consequential evolution of CNS loading and infection by HIV-1. There is an increased prevalence of latent HPV-DNA infection in HIV- infected patients[31]. It is significant that many viral infections are characterized by multifocal involvement of the CNS by groups of lymphocytes in the evolution of the integrally infectious state.

Transformation of cellular reactive responses: Dynamics of interaction of HIV infection with ongoing transformations in cellular reactive response would implicate lymphocyte depletion as an immunologically-mediated injury. Highly active antiretroviral therapy alone may be associated with a considerable rate of sustained tumor response[32]. It is perhaps in terms of a response primarily arising as a consequence of such injury that HIV infection would progress in its own right as a fundamentally transforming series of tissue and cellular reactivities. One might view this response to injury as a basic characterization of attributes paralleling the ongoing HIV infection. Primary effusion lymphomas specifically develop in association with Kaposi's sarcoma herpes virus infection, especially in HIV-infected individuals[33]. HIV-1 induces tumor angiogenesis and enhances KSHV transmission to target cells[34].

Clinical evidence suggests that the oncogenicity of HPV is altered by the HIV-1 infection irrespective of immune status. Progression of infection might be defined as an attribute arising directly from such evolving transformations in cellular and tissue reactivity that subsequently potentiate infections in general and HIV infection in particular.

Multiple opportunistic infections would perhaps potentiate further progressive infection by HIV in a manner linked particularly to immune suppressive effect and to depletion of various cellular elements in general. Expression of the EBV EBNA-2 open ending frame in oral epithelium may be related to development of oral hairy leukoplakia[35].

One would progressively suffer from a depletion of lymphocytes concurrent with overwhelming opportunistic infection arising in AIDS patients. Pathogenesis of HIV-associated lymphoma is multifactorial, involving particularly Epstein-Barr virus[36].

The very concept of selective T-cell helper depletion might account for variable response to the consequences of an HIV infection. Only insofar as it develops into AIDS does a basic scheme of defining pre-AIDS criteria help account for progressiveness as a transformation to the AIDS syndrome. An increased risk for HIV-associated nonHodgkin's lymphoma may possibly develop as a result of a combination of immunodeficiency, increased immune activation and HIV-insertional mutagenesis[37].

Malignancy that develops as HIV infection progresses is simply an expression of modulated depletion of various cellular pathways that invoke the subsequent emergence of viral infections as precarcinogenesis. Epstein-Barr virus DNA is present in lymphoma cells of HIV-infected patients and the EB virus load may be a marker of lymphoma in these patients[38].

A cycling pattern of HIV-1 turnover: Macrophages laden with HIV virions would implicate a cycling phenomenon of turnover reflected in replication of the virus, on the one hand and in incorporation of provirus within the cell genome, on the other. It might prove significant that a large virion load within macrophages would upset such a cycling phenomenon in specifically induced ways arising as involvement of the cell genome. RNA protein uncoupling appears a possible target in such contextual imbalance of virion-replicative events, implicating, paradoxically, the incorporation of provirus within the genome.

It might be significant that the outcome for viral replication is essentially a phenomenon linked to events of cellular injury.

Replication of virion would perhaps account only partially for such cellular injury in HIV infection. Inhibitors of the HIV aspartyl protease appear to have a direct anti-angiogenic and antineoplastic effect that is unrelated to antiviral activity[39].

One might perhaps regard virion replication an integral event in its own right that is independent of consequences of related cell injury.

Dynamics of injury of a virally infected cell would involve nuclear/cytoplasmic uncoupling. Indeed, only in terms of an uncoupling or dissociation of chain pathway or sequence events can one perhaps also explain a related injury to cells that otherwise proliferate in a neoplastic fashion, as seen, for example, with Epstein-Barr virus.

HIV would implicate cell injury in terms of consequential involvement of nuclear DNA and its transcription and translation processes in cell replication. Combined AIDS-Kaposi's sarcome involves cytokines such as Interleukin 6 driven by autocrine and paracrine

systems and human herpes virus 8. This virus encodes for open reading frames as homologs of proteins implicated in cellular regulation of proliferation, apoptosis and immune response[40].

Viral proteins function as growth factor ligands/receptors, signal transduction proteins, transcription factors and cell cycle regulators[41]. Inflammation and cytokine/chemokine production appear closely related to ongoing cell turnover that implicates macrophage and leukocyte cycling or turnover.

Neoplastic transformation: Neoplastic transformation would arise as a responsive but also autonomous phenomenon of inflammatory and cellular turnover events. The interactions between HIV and human papillomavirus, in particular, may favor progression of cervical neoplasia[42].

One would consider biology of malignancy as incorporating a cellular participation of events in a context of ongoing inflammatory consequences affecting cell cycling. Cell division would both arise and potentiate such malignant transformation borne out by inflammatory reactivity of tissues as integral organ pathobiology.

HIV participation in infections of the lymphoreticular system appears conducive to a series of transforming events affecting DNA and DNA/RNA transcription/translation events.

HAART administration to HIV + patients may prevent an increased risk for Kaposi's sarcoma and nonHodgkin's lymphoma[43].

A schematic representation of pathway consequences would implicate a further amplifying step in the subsequent development of clonal cell cycling. Indeed, one might equate cell cycling events with a clonality that evolves as a series of subcellular consequences of cytokine and chemokine induced injury to the genome.

Macrophages appear critically implicated in events as self-amplifying influence in inducing cell injury particularly affecting lymphocytes. Only in such pathway processes would there develop a sequential series of steps promoting self-amplification as a distinctively integral process in its own right. In the absence of Kaposi's sarcoma-associated herpes virus-associated diseases, latent infection of lymph nodes may provide a mechanism for persistent KSHV infection in KSHV/HIV-1 coinfection[44].

CONCLUSION

Replicative processes in cell division would perhaps participate in the development of anomalous characterization of transcription and translation of DNA and RNA that further progress as self-amplification of such anomalous events.

Indeed, anomalies of both consequence and effect might better characterize the neoplastic process as cytokine and chemokine events of induced derivation that both promote and further involve inflammation in consequential cell division and transformation of cell division cycling.

REFERENCES

1. Roberts, ES., E. Masliah and HS. Fox,2004. CD163 identifies a unique population of ramified microglia in HIV encephalitis (HIVE). J. Neuropath Exp. Neurol., 63:1255-1264.
2. Michaud, J., R. Fajardo, G. Charron, A. Sanvageen, F. Berrada, D. Remla, H. Dilhaydy, Y. Robitaille, A. Kessous-E-Elbaz, 2001. Neuropathology of NFH gp160 transgenic mice expressing HIV-1 Evn Protein in neurons. J. Neuropath Exp. Neurol. 60:574-587.
3. Macchetti, I. and A. Bachis, 2004. Brain-derived neurotrophic factor activation of TrkB protects neurons from HIV-1/gp120-induced cell death. Crit. Rev. Neurobiol., 16: 51-7.
4. Nashemy, RL., A. Bachis, E. Acques and I. Mocchetti, 2004. Human immunodeficiency virus type 1 glycoprotein gp120 reduces the levesl of brain-derived neurotrophic factor *in vivo* : Potential implications for neuronal cell death. Eur. J. Neurosci., 20: 2857-64.
5. Royal, W., M. Leander, YE. Chen, EO. Major, RP. Bissonnette, 2004. Nuclear receptor activation and interaction with morphine. J. Neuroimmunol., 157: 61-5.
6. Perry, SW., JP. Norman, A. Litzburg, D. Zhang, S. Dewhurst and HA. Gelbard, 2005. HIV-1 Transactivator of Transcripton Protein induces mitochondrial hyperpolarization and synaptic stress leading to apoptosis. J. Immunol., 174: 4333-44.
7. Petito, C., B. Roberts, JD. Cantando, A. Rabinstein and R. Duncan, 2001. Hippocamal injury and alterations in neuronal chemokine co-receptor expression in patients with AIDS. J. Neuropath Exp. Neurol., 60:377-385.
8. Khan, MZ., R. Brandimarti, JP. Patel, N. Huynh, J. Wang, Z. Huang, H. Fatatis and O. Meucci, 2004. Apoptotic and antiapoptotic effects of CXCR4: Is it a matter o intrinsic efficacy? Implications for HIV neuropathogenesis. AIDS Res. Hum. Retroviruses, 20: 1063-71.
9. Agius, LM., 2004. Is repetitive opportunistic infection in AIDS patients the effective mechanism for neurodegeneration in terms of endlessly amplifying cytokine/chemokine effect? Med. Hypotheses., 62: 587-92.

10. Bergunzini, V., S. Delbue, JY. Wang, K. Reiss, M. Prisco, S. Amini, K. Khalili and F. Peruzzi, 2004. HIV-Tat promotes cellular proliferation and inhibits NGF-induced differentiation through mechanisms involving Id1 regulation. Oncogene, 23: 7701-11.
11. Cartier, L., O. Hartley, M. Dubois-Druphin and KH . Krause, 2005. Chemokine receptors in the central nervous system: Role in brain inflammation and neurodegenerative disease" Brain Res. Brain Res. Rev., 48:16-42.
12. Bruce-Keller, A.J., A. Cheuben, FO. Dimayuga, J.J. Gee, JN. Keller and A. Nath, 2003. Synaptic transport of human immunodeficiency virus-Tat protein causes neurotoxicity and gliosis in rat brain. J. Neurosci., 23:8417-22.
13. Zhou, BY., Y. Liu, B. Kim, Y. Xiao, J. He, 2004. Astrocyte activation and dysfunction and neuron death by HIV-1 Tat expression in astrocytes. Mol. Cell Neurosci., 27: 296-305.
14. Pocernich, CB., D. Boyd-Kimball, HF. Pross, V. Thongboonkerd, BC. Lynn, JB. Klein, V. Catebrese *et al*., 2005. Proteomics analysis of human astrocytes expressing the HIV protein Tat. Brain Res. Mol. Brain. Res., 2005 133: 307-16.
15. Torres-Mimoz, J., P. Stockton, N. Tacoronte,B. Roberts, R. Maronpot and CK. Petito, 2001. Deletion of HIV-1 gene sequences in hippocampal neurons isolated from postmortem AIDS brains by laser capture microdissection. J. Neuropath Exp. Neurol., 60:885-892.
16. Spimillo, A., F. Zara, R. Zappatore, S. Cesari, C. Bergante and P. Morbini, 2004. Apoptosis-related proteins and cervical intraepithelial neoplasia in human immunodeficiency virus-seropositive women. Gynecol. Oncol., 95: 500-5.
17. Kanmogue, G., RC. Kennedy and P. Grammas, 2002. HIV-1 gp120 proteins and gp160 peptides are toxic to brain endothelial cells and neurons: Possible pathway for HIV entry into the brain and HIV-associated dementia. J. Neuropath Exp. Neurol., 61: 992-1000.
18. Krizanac-Bengez, L., MR. Mayberg, D. Janigro, 2004. The cerebral vasculature as a therapeutic target for neurological disorders and the role of shear stress in vascualr homeostasis and pathophysiology. Neurol. Res., 26 846-53.
19. Wiley, CA., C. Achim, R. Hammond, S. Love, E. Mashiah, L. Radhakrishman, V. Sanders and G.Wang, 2000. Damage and repair of DNA in HIV encephalitis. J. Neuropath Exp. Neurol., 59: 955-965.
20. Mattson, M., N. Haugley and A. Nath , 2005. Cell death in HIV dementia. Cell Death Diff.
21. Garden, G., W. Guo, S. Jayadev, C. Tum, S. Balcaitis, J. Choi, TJ. Montine, T. Muller and R. Morrison, 2004. HIV associated neurodegeneration requires p53 in neurons and microglia. Faseb. J., 18: 1141-3.
22. Khan, M.Z., R. Braudemarti, B.J. Musser, D.M. Resue, A. Fatatis and O. Meucci, 2003. The chemokine receptor CXCR4 regulates cell cycle proteins in neurons. J. Neurovirol., 9: 300-14.
23. Langford, D., A, Grigorian, R. Hurford, A. Adeine, RJ. Ellis, L. Hansen and E. Masliah, 2004. Altered P-glycoprotein expression in AIDS patients with HIV encephalitis. J. Neuropath Exp. Neurol., 63: 1038-1047.
24. Lee, G.a. and R. Bendayan,2004. Functional expression and localization of P-glycoprotein in the central nervous system: Relevance to the pathogenesis and treatment of neurological disorders. Pharm. Res., 21: 1313-30.
25. Gray, F., F. Chretien, AV. Vallat-Decouvelaere and F. Scaravilli, 2003. The changing pattern of HIV neuropathology in the HAART era. J. Neuropath Exp. Neurol., 62: 429-440.
26. Vallet-Decouvelaere, AV., F. Chretien, G. Gras, G. Le Pavec, D. Dormont and F. Gray, 2003. Expression of excitatory amino acid transporter-1 in brain macrophages and microglia of HIV-infected patients: A neuroprotective role for activated microglia?. J. Neuropath Exp. Neurol., 62: 475-485.
27. Monno, L., G.B. Zimatore, M. Di Stefano, A. Appice, P. Livria and G. Augarano, 1999. Reduced concentrations of HIV-RNA and TNF-alpha coexist in CSF of AIDS patients with progressive multiforcal leukoencephalopathy. J. Neurol. Neurosurg Psychiatry, 47: 367-373.
28. Rostasy, K., C. Egles, A. Chauhar, M. Kneisse, P. Bahran, C. Yiannoutsos, D. Hunter and A. Nath *et al*., 2003. SDF-1alpha is expressed in astrocytes and neurons in the AIDS Dementia Complex: An *in vivo* and in vitro study. J. Neuropath Exp. Neurol., 62: 617-626.
29. Boccolesco, S., R. Marenzi, H. Dahl, L. Vago, MR. Terreni, F. Broccolo, A. Lizzarin, Linde and P. Cingque, 1999. Human herpes virus 6. In: Cerebrospinal fluid of patients infected with HIV: Frequency and clinical significance. J. Neurol. Neurosurg. Psychiatry., 67: 789-792.
30. Daniel, D.C., Y. Kinoshita, M.A. Khan, L.D. Valle, K. Khelili, J. Rappaport and E.M. Johnson, 2004. Internalization of exogenous human immunodeficiency virus-1 protein Tat, by KG-1 oligodendroglioma cells followed by stimulation of DNA replication initiated at the JC virus origin. DNA Cell Biol., 23: 858-67.

31. Pelletier, F., C. Drobacheff-Thiebant, F. Aubin, A.G. Venier, E. Mirigin and R. Laurent. Effects of imiquimod on latent human papillomavirus anal infection in HIV-infected patients. Ann. Dermatol. Venereol., 131: 947-51.
32. Noy, A., D.T. Scadden, J. Lee, B.J. Dezube, D. Aboulefia, A. Tulpule, S. Walmsley and P. Gill, 2005. Angiogenesis inhibitor IM862F is ineffective against AIDS-Kaposi's sarcoma in a phase III trial, but demonstrates sustained potent effect of highly active antiretroviral therapy; from the AIDS malignanyc consortium and IM862 Study Team. J. Clin. Oncol., 23: 990-8.
33. Fan, W., D. Dubman, A. Chedburn, W.J Jr. Harrington, E. Cesarman and D.M. Knowles, 2005. Distinct subsets of primary effusion lymphoma can be identified based on their cellular gene expression profile and viral association. J. virol.,79: 1244-
34. Aoki, Y. and G . Tosato, 2004. Neoplastic conditions in the context of HIV-1 infection. Curr. HIV Res., 2: 343-9.
35. Walling, D.M., P.D. Ling, A.V. Gurdadze, C.M. Montes-Walters, Flaitz, C.M . Nichols, 2004. Expression of Epstein Barr virus latent genes in oral epithelium: Determinants of the pathogenesis of oral hairy leukoplakia. J. Infect. Dis., 190: 396-9.
36. Cheung, TW., 2004. AIDS-related cancer in the era of Highly Active Antiretroviral Therapy (HAART): A model of the interplay of the immune system, virus and cancer. On the offensivethe trojan horse is being destroyed. Part B: Malignant Lymphomas. Cancer Invest., 22: 787-98.
37. Killebrew, D. and B. Shiramizu, 2004. Pathogenesis of HIV-associated nonHodgkin lymphoma. Curr. HIV Res., 2: 215-21.
38. Fan, H., S.C. Kim, C.O. Chima, B.F. Israel, K.M. Lawless, P.A. Eagan and S. Elimore *et al.*, 2005. Epstein Barr viral load as a marker of lymphoma in AIDS patients. J. Med. Virol.,75: 59-69.
39. Monini, P., C. Sgadari, E. Toschi, G. Bariller and B. Ensoli, 2004. Antitumor effects of antiretroviral therapy. Nat. Rev. Cancer., 4: 861-75.
40. Cheung, TW., 2004. AIDS-related cancer in the era of Highly Active Antiretroviral Therapy (HAART): A model of the interplay of the immune system, virus and cancer. On the offensive—the Trojan horse is being destroyed Part A: Kaposi's sarcoma. Cancer Invest., 22: 774-86.
41. Direkze, S. and H. Laman, 2004, Regulation of growth signalling and cell cycle by Kaposi's sarcoma-associated herpes virus genes. Int. J. Exp. Pathol., .85: 305-19.
42. Moodley, M., 2005. Update on pathophysiologic mechanisms of human papillomavirus. Curr. Opin. Obstet. Gynecol., 17: 61-4.
43. Clifford, G.M., J. Polesel, M. Rickenbach, L. Dalmaso,O. Kerser, A. Kofler and E. Rapiti *et al.*, 2005. Cancer risk in the swiss HIV cohort study: Associations with immunodeficiency, smoking and highly active antiretroviral therapy. J. Natl. Cancer. Inst., 97: 425-32.
44. Campbell, T.B., KA. Staskine, J. Folkvoid, I.E. White, J. Neid, XQ. Zhang and E. Connick, 2005. Persistence of Kaposi Sarcoma-associated Herpes Virus (KSHV)-infected cells in KSHV-HIV-1 coinfected subjects without KSHV-associated diseases. J. Infect. Dis., 19: 367-71.