# Response to Valacyclovir in an HIV-infected Girl with Epstein Barr Infection

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Response of EBV infection to valacyclovir in HIV infected children has not been reported earlier. An 8 years old HIV infected girl with undetectable viral load and normal CD4 count on regular antiretroviral therapy presented with persistent fever, lymphadenopathy and pancytopenia due to Epstein Barr virus (EBV). The child responded to valacyclovir.

**Key words**: *Children, EBV, HIV, Valacyclovir.*

Primary Epstein Barr virus (EBV) infection can cause leucoplakia and variety of neoplasms such as EBV lymphoproliferative syndromes, nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin's lymphoma and a subset of EBV positive gastric carcinomas especially in immunocompromised patients [1,2]. In immunocompromised hosts, it may infect liver cells, neural cells and hematological cells other than lymphocytes leading to cytopenias [3]. It has been found that in HIV infected patients, highly active antiretroviral therapy (HAART) does not lead to decrease in EBV viremia even when HIV viral load becomes undetectable or CD4 count increases [4]. We report an HIV infected girl on HAART with undetectable viral load and normal CD4 counts who developed infectious mononucleosis with peripheral cytopenia and persistent fever that responded to valacyclovir.

## CASE REPORT

An 8 years old HIV infected girl presented with fever for 1 month, cough and ear discharge for 15 days. She had been treated for pulmonary tuberculosis 2 years back. She had been on antiretroviral therapy (ART) since past 1 year consisting of Zidovudine (AZT), Lamivudine (3TC) and Efavirenz (EFV). She was febrile, had insignificant axillary and cervical lymphadenopathy, splenomegaly and oral thrush. Other systems were normal. Investigations showed anemia and leucopenia (***Table* I**). Peripheral smear did not show any atypical lymphocytes. Her Chest *X*-Ray showed haziness in right lower zone. Blood culture, peripheral smear for malaria, optiMAL test, Widal test, urine, stool, sputum examinations were normal. Ear swab grew diphtheroids. Fundus examination was also normal. Her Weil Felix test, RA factor, ANA and anti-dsDNA were negative. Serial hemograms showed a trend of gradual pancytopenia (***Table* I**). USG Abdomen showed hepatosplenomegaly. Bone marrow examination showed hypocellular marrow with early fibrosis. Her CD4 count was 406/mm$^3$ (27.6%) with CD4:CD8 ratio of 1.63, and HIV viral load was undetectable. Her EBV viral capsid antigen (VCA) IgM was negative (0.61 Index) and Parvovirus IgM was also negative. Renal and liver function tests were normal. She was treated with IV antibiotics and fluconazole for 14 days to which pneumonia and oral thrush responded. However, she continued to be febrile and subsequently, on Day 40 of her fever, developed large cervical and axillary lymphadenopathy. Chest *X*-ray did not show any mediastinal widening. A lymph node biopsy was done which was suggestive of necrotizing lymphadenopathy. In view of persistent fever, pancytopenia and lymphadenopathy, she was suspected to have infectious mononucleosis and her repeat CMV IgM was done, which was negative. Her EBV viral capsid antigen IgM after 15 days was positive (1.12 Index). She was then treated with valacyclovir (10 mg/kg/dose TDS) for 12 days till anti-EBV VCA-IgM became negative. EBV

**TABLE I** SERIAL HEMOGRAM OF THE PRINT

| Hemogram | Day 7 | Day 15 | Day 30 | Day 35 |
|---|---|---|---|---|
| Hemoglobin (g/dL) | 7.7 | 9.8 | 6.4 | 5.8 |
| WBC (cells/cumm) | 3,400 | 2,600 | 2,100 | 1,300 |
| Polymorphs (%) | 40 | 66 | | |
| Lymphocytes (%) | 56 | 42 | | |
| Platelets (cells/cumm) | 2,46,000 | 2,73,000 | 1,83,000 | 59,000 |

nuclear antigen and EBV PCR were not done. She responded to the above treatment and fever subsided within 5 days of therapy and hemogram normalized within a week. On follow up, her hemogram continued to be normal, and she is asymptomatic and on regular ART.

## DISCUSSION

An antiviral drug that could reduce the severity of acute infectious mononucleosis and potentially lower the risk for serious sequelae would be highly desirable [5].

Several antiviral drugs inhibit replication of EBV in cell culture by targeting viral DNA polymerase including acidic nucleoside analogues caciclovir, ganciclovir, penciclovir as well as their prodrug- valacyclovir, valganciclovir and famciclovir, acyclic nucleotide analogues (cidofovir and adefovir) and pyrophosphate analogues (foscarnet) [1]. Despite their potency in vitro, these drugs have limited use in vivo for treatment of acute primary EBV infection as well as EBV associated malignancies due to toxicity and non-specific antiviral activities. The reason for antiviral failure may be that most of the symptoms and signs of acute EBV are not directly due to viral cytopathology in infected tissues, but to immunopathic responses to EBV-infected cells, particularly EBV-infected B-lymphocytes and also the levels of acyclovir achieved in the oropharynx, particularly after oral administration of the drug are inadequate as compared to titres that are produced by acyclovir given intravenously [1]. Valacyclovir is the L-valyl ester of acyclovir. This modification increases acyclovir bioavailability by 3- to 5-fold compared with oral acyclovir [6]. Pharmacokinetic data suggests that dose of valacyclovir regimen of about 30 mg/kg/day gives similar AUC as that with acyclovir given 250 mg/$m^2$ intravenously [7]. Due to its improved absorption with higher serum concentrations, this drug is preferable to acyclovir for the treatment of EBV infections [8]. Common adverse drug reactions associated with valacyclovir therapy are the same as for acyclovir, its active metabolite, and include: nausea, vomiting, diarrhea and headache [9].

The association of HIV and Epstein-Barr virus infection has been reported in children with lymphocytic interstitial pneumonia and lymphomas [9]. Peripheral cytopenia with persistent fever has rarely been reported in HIV infected children as was seen in our patient. A study from Minnesota has found valacyclovir to be effective in treating infectious mononucleosis where the drug lowered or eliminated EBV in research subjects who took it for two weeks [10]. Similarly in our patient, cytopenias and fever responded to valacyclovir following which EBV VCA IgM also became negative signaling latency of EBV in the child.

Studies of corticosteroids in infectious mononucleosis show amelioration of acute symptoms; however, the risks of prednisolone are only justified in severe disease, for example where there is incipient airway obstruction, where steroids may reduce the need for surgical intervention to protect the airway.

There have been no reports of response of EBV infection to valacyclovir in HIV infected children. Though we had a good response to valacyclovir in our patient, detailed studies are required to determine efficacy of valacyclovir to treat complicated infectious mononucleosis in HIV infected children.

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