HIV Cure: Are we there yet?

Dear Editor,

Human immunodeficiency virus (HIV) is a RNA retrovirus known for its ability to integrate in human genome, thus remain latent and persist lifelong. Though major breakthroughs have been achieved in field of HIV prevention and new cases have decreased over the years, we have 34 million people all over the world living with HIV waiting for the cure.[1] The recent advances and case reports has given all the hope that cure of HIV is indeed possible. Researchers are working on several strategies for virus eradication like eliminating latency, eliminating residual virus replication, enhance HIV specific immunity and making cells resistant to HIV.

Recent developments have materialized the concept that HIV cure is indeed possible. The popular Berlin patient, HIV positive man who have sex with man (MSM), who got CCR5Δ32/Δ32 allogeneic stem cell transplantation(SCT) for relapsed acute myeloid leukemia(AML) has now recovered his CD4+ T cells whereas HIV RNA and HIV DNA are undetectable and HIV viral antibodies are diminishing which the scientists are calling functional cure.[2-4] Another reported case is of Boston patients who were CCR5+(heterozygous) HIV+ underwent allogeneic SCT from CCR5+(WT) donor under reduced intensity irradiation for his lymphoma. They are reportedly HIV DNA –ve and HIV RNA-ve 4 years after transplant. Patient were during and after SCT on antiretrovirals.[5] Other than coreceptor status , graft vs host disease(GVHD) is thought to play significant role in clearing these stem cell recipients' HIV infected cells.[2-5]

Another interesting set of patients are 14 patients in Visconti cohort who were treated in acute HIV infection and continued on antiretroviral therapy(ART) for 3 years have not shown any viral rebound after stopping treatment.[6] This cohort has raised two issues (a) whether to start treatment early in every HIV infection in developing countries, where resources are scarce, to achieve functional cure, and (b) how does administered antiretrovirals lead to the observed effect. If the mechanism is prevention of establishment of viral reservoir, couldn't the reservoir be established after 3 years while the patients still have the virus? Or is it due to qualitative changes in virus or inherent dynamic host factors?

The other case is the report of a functional cure in an infant (Mississippi patient) with positive HIV DNA and RNA in blood on second day who was started on full antiretroviral regimen by 31 hours of life. The infant received antiretroviral till 18 months of age. Plasma viral load, peripheral blood mononuclear cell

DNA, and HIV-specific antibodies remained undetectable with standard assays at 26 months after birth thus achieving functional cure.[7]

The recent studies toward eliminating proviral latency, which has remained obstacle to HIV cure, with agents like vorinostat,[8] disulfiram[9] are promising. But the clinical translation is unlikely to bear fruit despite the exciting *in vitro* studies. Much talked nowadays is the use of zinc (Zn) finger nucleases as a gene therapy approach to "remove" the CCR5 co-receptor in circulating CD4 T cells in HIV infected individuals and reinfuse the modified cells into the patient.[10] This concept is based on findings of the Berlin patient . The study is still in its infancy and the outcome is eagerly awaited.

The application of SCT in each and every HIV patient is not feasible for a number of reasons. But nevertheless has opened new avenues for research like transfusing autologous "in vitro CCR5 removed" CD4+cells. The role of CXCR4 receptor unlike CCR5 on HIV cure is yet to be explained. What is feasible at current moment as Mississippi patient and Visconti patients have shown as far as cure is concerned is to identify and treat HIV patients early before viral reservoirs are well established . The limited success of HIV purging agents like vorinostat for HIV cure could lead to "future fatigue" in part of patient for it will give hope to patients initially, only to send them into the depths of despair later.

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