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Tackling HIV/AIDS - Are we there yet?

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It has been three decades since HIV has been discovered [1] and over seventeen years Antiretroviral Therapy (ART) has emerged as the first line of therapy to cure the disease that has affected millions of lives. Currently close to 34 million people around the globe are suffering with HIV/AIDS and over 8 million people are receiving ART in low and middle income countries [2]. ART has dramatically improved the expectancy and quality of life of HIV/AIDS victims. Nevertheless, current ART cannot get rid of HIV infection totally and requires lifelong adherence. ART administration is burdensome to the public health systems because of the cost associated with it. Hence there is a need for other possible treatment strategies for lifetime treatment to patients with affordable costs to health systems. Failure to eradicate HIV during ART indicates the inherent stability of the viral genome. Persistence of HIV in small pool of CD4+ T cells even under the viral suppression with ART establishes latency. The CD4+ T cells with stable and long-lived latent virus serve as a HIV reservoir. The permanence of the HIV reservoirs might be responsible for prolonged immune activation and inflammation observed in people with suppressed viremia, which, in line, may be associated with co-morbidities like cardiovascular events, renal insufficiency and hepatic failure [3]. A study by Ho et al. published in the journal Cell has shown that the latent viral reservoir is 60 times larger than previously believed [4]. Hence this reservoir poses threat for the complete eradication of HIV/AIDS.

Although advancements in the treatment of HIV infection and prevention approaches were made, development of an efficient vaccine holds the key for control and complete eradication of HIV. However, HIV vaccine development has suffered major setbacks. A total of six efficacy trials [5-10] for vaccines were conducted until now of which two trials were of recombinant bivalent gp120 protein exhibited no overall benefit, another trial with adenoviral Ad5 vaccine expressing Gag, Pol, and Nef proteins showed no intrinsic merit, one more trial of the same vaccine conducted in South Africa was discontinued and also shown to increase the risk of HIV infection in vaccine receivers. Exception to these trials one trial conducted in Thailand (RV144) for efficacy of priming recombinant canarypox vector vaccine (ALVAC-HIV [vCP1521]) with a booster doses of gp120 vaccine (AIDSVAX B/E) showed a modest efficacy of 31% [6], earlier this year trial of DNA prime recombinant adenovirus type 5 boost vaccine (DNA/rAd5) [11] was discontinued due to lack of efficacy. Although disappointing these trials would be informative for future vaccine trials.

Cases of sterilizing cure of HIV with no resurgence have been reported, one well documented case is of the "Berlin Patient" Timothy Brown reported by Hutter et al. in the New England Journal of Medicine [12]. HIV cure was achieved in this person by giving an allogeneic bone marrow transplant for acute myeloid leukemia from a HLA matched donor. The unrelated donor had a homozygous 32 bp deletion in the CCR5 gene resulting in an inactive protein giving resistance to HIV infection. No HIV was detected in peripheral blood, bone marrow and rectal mucosa after 20 months of ART discontinuation as assessed by RT-PCR for RNA and DNA PCR assays for proviral DNA [12]. The Berlin patient remains "HIV free" until this day. Different from Berlin patient two patients from Boston with HIV and lymphoma were given bone marrow transplantation with wild type CCR5 gene, chemotherapy and radiation while continuing on ART have seen disappearance of HIV DNA in blood and tissues [13], one patient stayed without a viral rebound for 15 weeks and the other one 7 weeks after stopping ART. Even though promising stem cell transplant is highly risky, complex and expensive procedure.

Cases of functional cure have also emerged. First case reported by Persaud et al. [14] was of a baby from Mississippi born to a HIV infected woman. The child started receiving ART 30 hours after birth and stopped after 18 months. The baby has not shown any detectable virus according to the researchers who do not have answer as to how the baby got cured. Further studies are needed to see if this eradication strategy of early antiretroviral therapy could be used for all neonates infected with HIV. 14 patients in France of the VISCONTI cohort starting ART at ten weeks post infection and stopping after 3 years have maintained undetectable level of HIV for an average of 7.5 years.

Recent updates in basic science, clinical science and prevention science from around the world were presented in the 7th International Aids Society (IAS) conference on HIV pathogenesis and treatment (IAS 2013) held in Kuala Lumpur. The new WHO guidelines for ART were announced and the key points were the recommendation for ART initiation at a CD4 countless than or equal to 500 cells/mm^3, up from 350 cells/mm^3 and that treatment should start right away to all expectant or breastfeeding women and all children under five years with HIV, whatever their CD4 count is [15]. In the basic science research session Casazza et al. reported identification of cells called "CD4 null cells" with high transcription of viral RNA which could be targets for HIV elimination [16]. A French group from INSERM described an analysis of a HIV positive group with undetectable viral load even though they are not on ART called "elite controllers" and three comparison groups, the study showed higher inflammation in elite controllers than the HIV negative people but lower than HIV positive people not on any treatment regime [17]. An Argentinian group has shown that Antibody-Dependent Cellular Cytotoxicity (ADCC) has significant involvement in host immune response against HIV [18]. Van Lunzen et al. from Germany found that T Follicular Helper cells (TFH) serve as reservoirs for HIV and support infection [19]. Another group from University of North Carolina has reported a broadly neutralizing antibody called 3B3 that is attached to a *Pseudomonas*-derived toxin, PE38, capable of activating cells in which HIV is hiding and kill them [20]. Similarly a group from Cambridge, Massachusetts reported that β-catenin inhibitors plus panobinostat stimulated CD4 T cells actively producing HIV with double the potency on cells inactivated by panobinostat [21]. These could be potential strategies for eradication as they lure out the hiding latent HIV.

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The reports of both sterilizing and functional cure in few patients have given hope to many people around the world that a cure is possible. Scientific advancements discussed here are road maps for an HIV/AIDS free world. One major bottleneck in achieving a cure is the latent viral reservoir, the studies by Buzon et al. [21] and Denton et al. [20] are promising strategies to eliminate the latent HIV reservoirs. Approaches like re-activating latent HIV genome to, suppress residual virus replication and boosting host mediated clearance of reservoirs are also important strategies to abolish the virus and virus-infected cells. Another major setback is the failure to develop an effective vaccine, the failed efficacy trials informed us what might not have worked and what might have. Broadly neutralizing antibodies and using new replicating vectors might be couple of options for the next generation of HIV vaccines. Emergence of ART made HIV/AIDS more a chronic condition and long-term HIV patients on ART have higher risk of fostering co-morbidities like cardiovascular diseases, renal failure, etc. Research and support should also concentrate on identifying the link between HIV-treatment and aging to warrant a healthful old age in ART-treated patients with HIV. As known to most of us prevention is the best cure, preventive strategies like enhanced HIV testing, circumcision, and Prevention of Mother-to-Child Transmission (PMTCT) are also valuable. Finally the war against HIV/AIDS will only be won by collaborative effort between researchers, clinicians, policy makers and community leaders. As of now, the best way to curb HIV is early initiation of ART and prevention.

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