

Cure of human immunodeficiency virus/acquired immune deficiency syndrome: promising future prospects at horizon

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ABSTRACT

Acquired immune deficiency syndrome (AIDS) is a disease caused by human immunodeficiency virus and characterized by profound immunosuppression that leads to opportunistic infections, secondary neoplasms, and neurologic complications. AIDS is among the leading causes of death worldwide. Current therapeutic options are directed only toward management of AIDS, but not toward its prevention or cure. In addition, it also possesses numerous problems like drug resistance, drug toxicity, drug interactions, non-adherence to therapy, life-long and expensive treatment, etc. Recent years in drug development have shown promising prospects for prevention/treatment/cure of AIDS like histone deacetylase inhibitors, Vpu ion channel inhibitors, viral decay acceleration, maturation inhibitors, tat antagonists, gene/stem cell therapy, and antiretroviral vaccines.

Keywords: Antiretroviral therapy, Belinostat, Bevirimat, Valproic acid, National Acquired Immune Deficiency Syndrome Control Organization, Targeted therapies

INTRODUCTION

Thirty four years after acquired immune deficiency syndrome (AIDS) was described, there are an estimated 35 million people living with human immunodeficiency virus (HIV) globally with the highest prevalence in sub-Saharan Africa.¹ According to WHO report in 2013, 2.1 million people became newly infected with HIV.¹ In India, prevalence of AIDS is 0.27% with 2.08 million people living with AIDS.²

Current therapeutic options for AIDS include transcription inhibitors, protease inhibitors, entry inhibitors, and integrase inhibitors. But this therapy is not curative, and it also poses many challenges like drug resistance, drug toxicity, non-adherence, drug interactions, etc.

In recent years, frequency of single and multi-drug resistant HIV strains has increased significantly which impacts our current preventive and therapeutic strategies.³ Durability of first-line antiretroviral therapy (ART) regimen is about 2.5 years with drug toxicity (49%) being major reason for its modification.⁴ Non-adherence to ART due to polypharmacy, high pill burden is one more limitation of currently available options. It leads to loss of virologic control, the emergence of resistance and ultimately loss of future options.⁵ As most of available antiretroviral drugs are metabolized by CYP 3A4, 2C9 isoenzymes, they interact with other drugs like anti-tuberculosis or antifungals, etc., causing more adverse effects and complications.⁶ All these problems of existing therapies demands development of new drugs with increased efficacy while minimizing adverse effects and cost and duration of therapy.

Over a period of last few years many new molecules/strategies with novel mechanisms of action like histone deacetylase inhibitors (HDACI), uncoating inhibitors, maturation inhibitor, gene therapy, etc., have been identified and are under extensive research for treatment/cure of HIV/AIDS.

NEWER THERAPEUTIC OPTIONS

HDACI

Although effective combination ART (cART) has transformed HIV infection from an invariably fatal disease to a chronic illness, cART does not eradicate HIV infection. Even in the absence of undetectable plasma viral RNA, HIV persists in long-lived resting memory CD4 + T-cells, astrocytes and macrophages by establishing a “latent” infection. Latently infected cells are a major reservoir for HIV and represent a significant barrier preventing access to HIV DNA to ART.⁷

HDAC is an enzyme that maintains the latency of HIV by inhibiting viral transcription. HDACI (vorinostat, belinostat, givinostat, panobinostat, romidepsin, valproic acid) are being evaluated in a “shock-and-kill” therapeutic approach to reverse HIV latency. Using this approach, HDACI have induced HIV RNA synthesis in latently infected cells from some patients. These drugs expose the previously latent HIV-infected cells to the effects of anti-retroviral drugs.⁷

Administration of the HDACI vorinostat was well-tolerated in patients on cART and, in one study, induced a 4.8-fold increase in HIV RNA expression in their resting CD4 + T-cells. However, a major clinical concern with this strategy is that, although administered in the context of cART, infection of new uninfected CD4 + T-cells, and macrophages by induced virus during periods of viral activation from latency may occur. The hope is that the increase in viral production will lead to killing of the infected cell either by the virus itself or by the patient’s immune system or cART – A “sterilizing cure.” Currently, HDACI is in Phase II of clinical trial.⁸

Vpu ion channel inhibitors

Vpu channels are viroporins. Vpu is a small phosphorylated integral membrane protein encoded by the HIV Type 1 genome and found in the endoplasmic reticulum and Golgi membranes of infected cells. It has been linked to roles in virus particle budding and degradation of CD4 in the endoplasmic reticulum.⁹

It has been observed that Vpu deletion reduces number and infectivity of virus particles. Inhibitors of the Vpu ion channel are effective at interfering with viral replication in macrophages, a reservoir not targeted by currently available drugs.¹⁰

The lead compound, BIT225, showed potent anti-retroviral activity in Phase I study. BIT225 represents a first-in-class drug targeting HIV-1 within the monocyte-macrophage reservoir. BIT225, demonstrates encouraging anti-HIV-1 activity in our primary human CD14+ monocyte-derived macrophages (MDM) assay with >90% inhibition of HIV-1 release as measured by RT and p24.

BIT225 inhibits HIV-1 release from chronically infected MDMs. inhibits HIV-1 transmission to CD4 + T-cells. It affects Vpu ion channels of HIV-1 with no effect on HIV-2. It has no effect on reverse transcription or on the RT or protease enzymes and exerts its effects post-integration. BIT225 has shown promising results in Phase IIa and is under further evaluation.¹¹

Uncoating inhibitors

HIV uncoating is defined as the loss of viral capsid that occurs within the cytoplasm of infected cells before entry of the viral genome into the nucleus. It is an obligatory step of HIV1 early infection and accompanies the transition between reverse transcription complexes, in which reverse transcription occurs, and preintegration complexes, which are competent to integrate into the host genome.^{12,13} The tripartite motif 5alpha (TRIM5α) protein is a dominant factor of intrinsic immunity that mediates cellular restriction against retroviral infections in a species-specific manner and was originally discovered as a determinant of the resistance of monkey cells to HIV1 infection. But, the human version of TRIM5α does not target HIV-1. TRIM5α protein contains four domains: RING domain, Bbox 2 domain, coiledcoil domain, and B30.2 domain (SPRY) domain. All of the domains are necessary for efficient retrovirus restriction, and the B30.2 domain has been shown to be the determinant of the specificity of restriction. Although the exact mechanisms that lead to virus inactivation by TRIM5α proteins remain unclear, it is known that TRIM5α targets intact retroviral capsids early in viral replication prior to reverse transcription, by interacting directly with these through its B30.2 (SPRY) Cterminal domain. Currently, TRIM5α and its variants are under extensive research to make human cells resistant to HIV infection.¹²⁻¹⁴

Maturation inhibitors

Maturation is a process by which virion changes the structure and becomes infectious. Viral maturation begins concomitant with (or immediately following) budding, and is driven by viral PR cleavage of the Gag and Gag-Pro-Pol polyproteins at 10 different sites, ultimately producing the fully processed MA, CA, NC, p6, PR, RT, and IN proteins. Over the course of maturation, these processed proteins rearrange dramatically to create the mature infectious virion.¹⁵⁻¹⁷

Bevirimat is a novel HIV-1 maturation inhibitor with a mechanism of action that is distinct from other anti-retroviral

agents. Specific inhibition of the final rate-limiting step in Gag processing by bevirimat prevents the release of mature capsid protein from its precursor (CA-SP1), resulting in the production of immature, non-infectious virus particles. Bevirimat inhibits replication of both wild-type and drug-resistant HIV-1 isolates. Bevirimat has completed Phase II studies and demonstrated a robust dose-dependent reduction in viral load ($>1.5 \log_{10}$ copies/ml). Short-term administration (≤ 14 days) of bevirimat is well tolerated, even when used in combination with other anti-retroviral agents. After rapid oral absorption plasma concentrations decreased in a log-linear manner with a mean plasma elimination half-life ranging from 58 to 80 hrs; the long half-life of bevirimat supports once-daily dosing. Study results from a Phase I study of another maturation inhibitor vivecon in HIV-negative participants found the drug to be safe, with good bioavailability.¹⁵⁻¹⁷

Tat antagonists

Tat is a protein that is encoded for by the tat gene in HIV-1. Tat is a regulatory protein that drastically enhances the efficiency of viral transcription. Tat is required for transcription initiation and/or elongation, depending on the basal activity of the HIV-1 long terminal repeat promoter.¹⁸⁻²⁰

Ro-3335 and Ro 24-7429 have been shown to inhibit replication of HIV-1 in acute and chronically infected cells, to reduce steady state viral RNA in chronically infected T-lymphocytes, and to partially restore CD4 expression in infected T-lymphocytes.¹⁸⁻²⁰

Viral decay acceleration

The deoxycytidine analog KP1212, and its prodrug KP1461, are prototypes of a new class of anti-retroviral drugs acting by a unique mechanism of action of viral decay acceleration. They are designed to increase viral mutation rates way higher, with the goal of eventually causing the collapse of

the viral population. It works by accelerating viral mutation so much that HIV is disabled – A mechanism dubbed “lethal mutagenesis” or “error catastrophe.”²¹ It also appears to be generally safe and well-tolerated based on results from more than 80 patients who have received the drug. While larger studies are obviously needed, the conclusions from this paper certainly underscore the potential for positive clinical effects. This should encourage further development of the vascular disrupting agent mechanism as a new approach for the treatment of HIV-1 infection.²¹

Translation inhibitors

Many plants contain ribosome inactivating proteins (RIPs) like trichosanthin with N-glycosidase activity, which depurinate large ribosomal RNA and arrest protein synthesis. RIPs so far tested inhibit replication of mRNA as well as DNA viruses and these proteins, isolated from plants, are found to be effective against a broad range of viruses such as HIV, hepatitis B virus, and herpes simplex virus. The exact mechanism of antiviral activity is still not clear. But, it is thought to follow inactivation of the host cell ribosome, leading to inhibition of viral protein translation, and host cell death. Enzymatic activity of RIPs is not limited to depurination of the large rRNA, in addition, they can depurinate viral DNA as well as RNA. Recently, Phase I/II clinical trials have demonstrated the potential use of trichosanthin for treating patients with HIV disease.^{22,23}

Gene therapy zinc-finger nucleases (ZFN)

HIV-1 infected individuals can harbor viral isolates that can use CCR5, as well as CXCR4 receptors for viral entry. ZFN is an artificial restriction enzyme. ZFNs function as molecular scissors that cut a specific region of DNA. Then, the cell's own mechanism repairs this cut, often introducing mutations that result in a non-functional protein that does not allow binding and entry of virus into the host cell. Currently, this strategy is in experimental stages.²⁴⁻²⁶

Table 1: Newer therapeutic options.

Drug class	Target	Action	Current phase of development
HDACI	Latent infected CD4 cells	Expose previously latent HIV-infected cells to effects of ART	II
Vpu ion channel Inhibitors	Viral replication in macrophages	Reduces number and infectivity of virus particles	II
Uncoating inhibitors	Viral capsid	Making human cells resistant to viral entry	Preclinical
Maturation inhibitors	Gag protein	Prevents maturation and release of precursor virions	II Complete
Tat antagonists	Tat protein	Inhibition of transcription	I
Viral decay acceleration	Viral DNA	Lethal mutagenesis	Preclinical
Translation inhibitors	Ribosome	Arrest protein synthesis	II
ZFN	CCR5/CXCR4	Restriction enzyme	Preclinical

HDACI: Histone deacetylase inhibitors, ART: Antiretroviral therapy, ZFN: Zinc finger nucleases

OTHER THERAPEUTIC STRATEGIES IN PIPELINE

- CCR5 Δ 32 stem cell transplantation
- Immunotherapy with interleukin - 2, 7, 15, 21
- Vaccines.

CONCLUSION

The various upcoming molecules directed against the HIV virus work by novel mechanisms of action. Most of these new therapies are still in early developmental stages. However, the progress made so far in deciphering HIV pathogenesis and stages of viral infectivity is a definite advancement. Further, research and development in this field will bring newer targets and molecules acting on them to the forefront. The deduction of a cure for HIV may therefore not be such a distant dream after all.

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