The History of HIV Treatment: Antiretroviral Therapy and More

Md.S.Kalantari

HIV history timeline

- 1981:

  The first cases of severe immunodeficiencies were reported to the CDC.

- 1982:

  The CDC used the term AIDS, or acquired immune deficiency syndrome, for the first time.

- 1983:

French scientists at the Pasteur Institute discovered the virus that causes AIDS.

- 1986:

The virus causing AIDS was officially named HIV, or human immunodeficiency virus.

- 1987:

The FDA approved Zidovudine (AZT), the first antiretroviral drug used to treat HIV.

- 1996:

Highly active antiretroviral therapy (HAART) hit the market, boosting the life expectancy of someone with HIV by 15 years.

- 2007:

Timothy Ray Brown, known as the “Berlin patient,” got a bone marrow transplant to treat his leukemia. A few months later, doctors could no longer detect HIV in his blood despite no longer being on ART. He is the first person thought to be “cured” of cancer. (Though, there is no proven cure for HIV.)

- 2010:

A study found evidence that pre-exposure prophylaxis (PrEP) works. Researchers found that taking a daily dose of antiretrovirals not only helped those with HIV but also protected people without HIV from getting the virus.

- 2012:

The FDA approved the first at-home HIV test and the drug Truvada, a once-daily PrEP pill.

- 2021:

The FDA approved cabotegravir and rilpivirine (Cabenuva), the first long-acting shot used as a complete HIV treatment regimen.

NRTI`S

- Zidovudine (AZT, Retrovir): 1987
- Lamivudine (3TC, Epivir): 1995
- Abacavir (Ziagen): 1998
- Tenofovir disoproxil fumarate (Viread): 2001
- Emtricitabine (Emtriva): 2003

NNRTI'S

- Nevirapine (Viramune): 1996
- Efavirenz (Sustiva): 1998
- Etravirine (Intelence): 2008
- Rilpivirine (Edurant): 2011
- Nevirapine extended-release (Viramune XR): 2011
- Doravirine (Pifeltro): 2018
- Rilpivirine for ages 2 and up (Edurant PED): 2024

PI'S

- Saquinavir (Invirase): 1995
- Ritonavir (Norvir): 1996
- Indinavir (Crixivan): 1996
- Nelfinavir (Viracept): 1997
- Lopinavir/ritonavir (Kaletratra): 2000
- Atazanavir (Reyataz): 2003
- Fosamprenavir (Lexiva): 2003
- Tipranavir (Aptivus): 2005
- Darunavir (Prezista): 2006

Integrase Inhibitors

- Raltegravir (Isentress, Isentress HD): 2007
- Dolutegravir (Tivicay, Tivicay PD): 2013
- Bictegravir : 2018
- Cabotegravir (Vocabria): 2021

Recommended Initial Regimens for Most People With HIV

For people who do not have a history of using CAB-LA as PrEP, one of the following regimens is recommended[a]:

- BIC/TAF/FTC **(AI)**
- DTG plus (TAF or TDF)[b] plus (FTC or 3TC) **(AI)**
- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available.

For people who have a history of CAB-LA use as PrEP, INSTI genotype resistance testing should be performed before starting ART. If ART is to be started before results of genotypic testing results, the following regimen is recommended:

- DRV/c[c] or DRV/r with (TAF or TDF)[b] plus (FTC or 3TC)—pending the results of the genotype test **(AIII)**

- More long-acting drugs
- Immunotherapies:
- T-cell based therapies
- Immunomodulatory agents to enhance T-cell function
- Antibody targeting of the HIV reservoir
- Therapeutic vaccines that help your immune system fight HIV
- Genetically engineered HIV-resistant immune cells

FDA Approves Cabenuva and Vocabria for the Treatment of HIV-1 Infection

- CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use.
- VOCABRIA (cabotegravir) 30 mg tablets which should be taken in combination with oral rilpivirine

- in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

Antibody targeting of the HIV reservoir

nature communications

Article

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Trispecific antibody targeting HIV-1 and T cells activates and eliminates latently-infected cells in HIV/SHIV infections

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Check for updates

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Agents that can simultaneously activate latent HIV, increase immune activation and enhance the killing of latently-infected cells represent promising approaches for HIV cure. Here, we develop and evaluate a trispecific antibody (Ab), N6/αCD3-αCD28, that targets three independent proteins: (1) the HIV envelope via the broadly reactive CD4-binding site Ab, N6; (2) the T cell antigen CD3; and (3) the co-stimulatory molecule CD28. We find that the trispecific significantly increases antigen-specific T-cell activation and cytokine release in both $CD4^+$ and $CD8^+$ T cells. Co-culturing $CD4^+$ with autologous $CD8^+$ T cells from ART-suppressed HIV^+ donors with N6/αCD3-αCD28, results in activation of latently-infected cells and their elimination by activated $CD8^+$ T cells. This trispecific antibody mediates $CD4^+$ and $CD8^+$ T-cell activation in non-human primates and is well tolerated in vivo. This HIV-directed antibody therefore merits further development as a potential intervention for the eradication of latent HIV infection.

- Agents that can simultaneously activate latent HIV, increase immune activation and enhance the killing of latently-infected cells represent promising approaches for HIV cure

- targets three independent proteins: (1) the HIV envelope via the broadly reactive CD4-binding site Ab, N6; (2) the T cell antigen CD3; and (3) the co-stimulatory molecule CD28

Monoclonal Antibody

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MINIREVIEW

Ibalizumab, a Novel Monoclonal Antibody for the Management of Multidrug-Resistant HIV-1 Infection

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ABSTRACT Limited antiretrovirals are currently available for the management of multidrug-resistant (MDR) HIV-1 infection. Ibalizumab, a recombinant humanized monoclonal antibody, represents the first novel agent for HIV-1 management in over a decade and is the first monoclonal antibody for the treatment of MDR HIV-1 infection in combination with other forms of antiretroviral therapy in heavily treatment-experienced adults who are failing their current antiretroviral regimen. Ibalizumab demonstrates a novel mechanism of action as a CD4-directed postattachment inhibitor and has a favorable pharmacokinetic profile that allows for a dosing interval of every 14 days after an initial loading dose. Clinical studies have demonstrated reasonably substantial antiretroviral activity with ibalizumab among a complex patient population with advanced HIV-1 infection who are receiving an optimized background regimen, where limited therapeutic options exist. Ibalizumab was well tolerated in clinical trials, and the most common adverse effects included diarrhea, nausea, dizziness, fatigue, pyrexia, and rash. Resistance to ibalizumab has also been observed via reduced expression or loss of the potential N-linked glycosylation sites in the V5 loop of the envelope glycoprotein 120. The mechanism of action, pharmacokinetic parameters, efficacy, and safety of ibalizumab present an advance in the management of MDR HIV-1 infection. Future studies and postmarketing experience will further determine longer-term clinical efficacy, safety, and resistance data for ibalizumab.

Therapeutic vaccines that help your immune system fight HIV

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Therapeutic Vaccines for the Treatment of HIV

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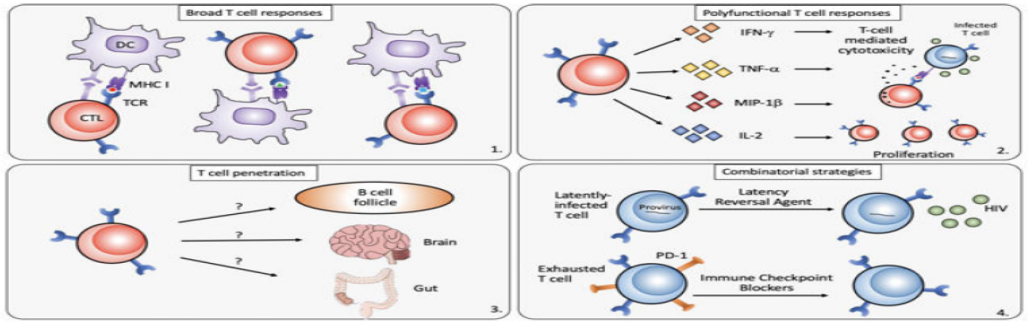
Abstract

Despite the success of anti-retroviral therapy (ART) in transforming HIV into manageable disease, it has become evident that long-term ART will not eliminate the HIV reservoir and cure the infection. Alternative strategies to eradicate HIV infection, or at least induce a state of viral control and drug-free remission are therefore needed. Therapeutic vaccination aims to induce or enhance immunity to alter the course of a disease. In this review we provide an overview of the current state of therapeutic HIV vaccine research and summarize the obstacles that the field faces while highlighting potential ways forward for a strategy to cure HIV infection.



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Article

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Immunogenicity of 2 therapeutic mosaic HIV-1 vaccine strategies in individuals with HIV-1 on antiretroviral therapy

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Mosaic HIV-1 vaccines have been shown to elicit robust humoral and cellular immune responses in people living with HIV-1 (PLWH), that had started antiretroviral therapy (ART) during acute infection. We evaluated the safety and immunogenicity of 2 mosaic vaccine regimens in virologically suppressed individuals that had initiated ART during the chronic phase of infection, exemplifying the majority of PLWH. In this double-blind, placebo-controlled phase 1 trial (IPCAVD013/HTX1002) 25 ART-suppressed PLWH were randomized to receive Ad26.Mos4.HIV/MVA-Mosaic (Ad26/MVA) ($n = 10$) or Ad26.Mos4.HIV/Ad26.Mos4.HIV plus adjuvanted gp140 protein (Ad26/Ad26+gp140) ($n = 9$) or placebo ($n = 6$). Primary endpoints included safety and tolerability and secondary endpoints included HIV-specific binding and neutralizing antibody titers and HIV-specific T cell responses. Both vaccine regimens were well tolerated with pain/tenderness at the injection site and fatigue, myalgia/chills and headache as the most commonly reported solicited local and grade 3 systemic adverse events, respectively. In the Ad26/Ad26+gp140 group, Env-specific IFN-γ T cell responses showed a median 12-fold increase while responses to Gag and Pol increased 1.8 and 2.4-fold, respectively. The breadth of T cell responses to individual peptide subpools increased from 11.0 pre-vaccination to 26.0 in the Ad26/Ad26+gp140 group and from 10.0 to 14.5 in the Ad26/MVA group. Ad26/Ad26+gp140 vaccination increased binding antibody titers against vaccine-matched clade C Env 5.5-fold as well as augmented neutralizing antibody titers against Clade C pseudovirus by 7.2-fold. Both vaccine regimens were immunogenic, while the addition of the protein boost resulted in additional T cell and augmented binding and neutralizing antibody titers. These data suggest that the Ad26/Ad26+gp140 regimen should be tested further.

Genetically engineered HIV-resistant immune cells

CURRENT OPINION

Advances in cell and gene therapy for HIV disease: it is good to be specific

C. David Pauza[a], *Kelly Huang*[a], *and Jose Bordon*[b]

Purpose of review
Tremendous advances in cell and gene therapy may soon realize the goal of treating and possibly curing HIV disease. These advances rely on new technologies for cell engineering and new strategies for product manufacturing that are targeting the most important immune deficits in HIV and promising to reconstitute protective, antiviral immunity and achieve natural suppression of HIV disease.

Recent findings
We summarize important advances in vectored passive immunity, e.g., directing *in vivo* expression of protective antibodies or antiviral proteins, B cell engineering to overcome the inadequate humoral immune response to HIV, and T cell engineering that is breaking new ground using viral vector modification of HIV specific T cells. These innovative approaches build on a substantial history of gene and cell therapy research in HIV disease.

Summary
Cell and gene therapy for HIV disease has been an area of tremendous innovation during the nearly two decades since early reports showed evidence for modulating disease. Recent efforts are building on the early experiences, closing gaps in previous approaches, and moving closer to effective treatment. Products approaching or already in clinical trials hold great promise for achieving durable suppression of HIV that will revolutionize therapy and offering hope to infected individuals that disease may be controlled without lifelong dependence on antiretroviral medications.

Video abstract
http://links.lww.com/COHA/A15.

Keywords
B cell engineering, cell and gene therapy, T cell engineering, vectored passive immunity, virus-specific T cell

thanks for your attention