Chinese Medical Journal®

Advances and challenges in antiretroviral therapy for acquired immunodeficiency syndrome

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Since its first isolation in 1983, human immunodeficiency virus (HIV) has caused nearly 50 million deaths and affected millions of people worldwide. Combination antiretroviral therapy (ART) has been universally recommended for HIV infection owing to its beneficial effects on the replication and transmission control of HIV.[1] The World Health Organization eliminated the traditional CD4-based ART eligibility requirements in late 2015. Thus, ART is now recommended for all people living with HIV (PLWH) regardless of the CD4 level or clinical stage. Global declarations called for a 75% reduction in new HIV infections and acquired immunodeficiency syndrome (AIDS) deaths between 2010 and 2020 and an end to the HIV/AIDS epidemic by 2030 through achieving the 90-90-90 targets (90% of PLWH are diagnosed, of whom 90% are on treatment, of whom 90% are virally suppressed) set for 2020 by the Joint United Nations Programme on HIV/AIDS.[2] Although positive progress toward achieving these targets was observed in 2019, substantial gaps remain. It was estimated that globally 79% (67%–92%) of all PLWH know their status, 78% (69%–82%) of those who know their status are undergoing treatment, and 86% (72%–92%) of those on treatment have suppressed viral loads. Globally, an estimated 37.9 million (32.7–44.0 million) PLWH, with 1.7 million (1.4–2.3 million) new infections and 770,000 (570,000 to 1.1 million) AIDS-related deaths in 2018. A series of government-sponsored, multi-center studies have been performed over the years to guide the optimization of the HIV/AIDS treatment approach for HIV/AIDS patients, and some new advances have emerged.[2]

Rapid-start and Test-and-treat Strategies

Rapid initiation of antiretroviral therapy (rapid ART), as early as the day of HIV diagnosis, is a strategy for increasing global interest to control the HIV epidemic and optimize the health of PLWH. Rapid ART is believed to be a key approach in reaching the 90-90-90 targets of the Joint United Nations Programme on HIV/AIDS for two main reasons. First, it can help control the HIV epidemic; second, it can optimize the health of PLWH. Based on accruing evidence from randomized clinical trials and observational cohorts, the prevention action campaign launched the "U = U" (undetectable = untransmittable) campaign to publicize the preventative benefits of ART in 2016. Several investigations on ART for the prevention of HIV infection have demonstrated an impact on the HIV care cascade.[3]

Rapid-start ART, including same-day ART, has been adopted by several programs in low- and middle-income countries and some high-income countries. However, there is currently insufficient evidence for establishing guidelines to recommend universal test-and-treat strategies for all people in all settings diagnosed with HIV. Consequently, there is a pressing need to conduct high-quality studies investigating immediate ART initiation. The context and structure of rapid start programs are important and there may be a disadvantage to same-day start for some individuals. Furthermore, areas in which messaging should be clearer, including that U = U is about sexual transmission of HIV and not transmission through breastfeeding or needle sharing, and that U = U prevents HIV but not other sexually transmitted infections.

Novel Antiretroviral (ARV) Agents and Regimens

Currently, the Food and Drug Administration (FDA) has approved more than 30 individual antiretroviral (ARV) agents and more than 10 coformulated combination products applied in the treatment of HIV. For most regimens guidelines suggested are commence of an

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001226

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Chinese Medical Journal 2020;133(23)

Received: 20-06-2020 **Edited by:** Peng Lyu

integrase strand transfer inhibitor (INSTI) and two nucleoside reverse transcriptase inhibitors (NRTIs). Preference often falls on the newer second-generation INSTIs dolutegravir (DTG) and bictegravir owing to their strong impedance to resistance, favorable side effects, and non-requirement of a pharmacologic booster. The ART regimens currently available are highly efficacious and well-tolerated. However, despite these advances in ART, drug-induced, and transmitted resistance and variable adherence to daily tablets remain challenges in the field. The development of novel ARV agents and preparations with extended-release formulations and limited toxicity profiles is needed to address these gaps in the HIV treatment toolbox.[4,5]

Capsid assembly (CA) inhibitors

The integral role of CA in both replication and virion maturation makes it a promising target for drug development. GS-6207 is an HIV-1 CA inhibitor delivered via subcutaneous injection; it inhibits virus production by inhibiting several steps of viral replication, including CA, capsid disassembly, and nuclear transport. Drug concentrations were detected at 24 weeks after a single injection, and most doses exceeded the 95% effective concentration for 12 weeks or longer. Moreover, GS-6207 retained activity against a broad range of HIV-1 mutants resistant to other ART classes, including those with Gag polymorphisms conferring resistance to maturation inhibitors (MIs). Furthermore, it exhibits activity against HIV-2.[5]

MIs

MIs bind to Gag and prevent proteolytic cleavage between p24 and spacer peptide 1 of the Gag polyprotein, inhibiting the production of mature virions. New data on GSK3532795 (formerly known as BMS-955176), a second-generation MI that exhibits a robust antiviral activity at doses from 50 to 200 mg daily, was presented publicly at Conference on Retroviruses and Opportunistic Infections (CROI) 2019.[4,5]

Nucleoside reverse transcriptase translocation inhibitors (NRTTIs)

In contrast to NRTI, NRTTIs have dual mechanisms of action: a 4′-ethynyl group inhibits translocation and in combination with a 3′-hydroxyl group induces chain termination. Islatravir (formerly known as MK-8591) is a first-in-class NRTTI that demonstrated much higher inhibitory quotients for both wild-type and NRTI-resistant HIV subtypes than tenofovir disoproxil, tenofovir alafenamide, zidovudine, and lamivudine (3TC). The tolerability and favorable pharmacokinetic profile of islatravir-eluting implant are of great significance for pre-exposed prophylaxis pre-exposure prophylaxis (PrEP), if in a combination of additional agents.

In addition, great achievements have been made on broadly neutralizing antibodies (bnAbs), fusion inhibitors (FI), attachment inhibitors (AI), and non-nucleoside reverse transcriptase inhibitors (NNRTIs). PGT121 is a human immunoglobulin G1 antibody targeting the V3 epitope in the envelope (Env); it exhibits potent neutralizing activity against 60% to 70% of global HIV-1 isolates according to the data from CROI 2019.[4] Albuvirtide (ABT), a novel FI with a similar mechanism of action to T20, has an extended half-life of 12 days and has been approved in China in 2018. Currently, a phase II trial to evaluate ABT in combination with 3BNC117 (a bnAb) as a long-acting (LA) maintenance combination in virologically suppressed PLWH is currently underway in the USA. Fostemsavir, a first-in-class AI, prevents HIV entry into CD4 T cells by binding to the viral envelope gp120 and is approved for compassionate use in heavily treatment-experienced adults with multi-drug-resistant HIV-1. Elsulfavirine (VM-1500, the pro-drug of VM-1500A) is a next-generation, highly selective NNRTI that was approved in Russia in 2017; however, it has not yet obtained regulatory approval in the USA.[5]

LA ART, which includes parenteral agents, implants, and patches, is likely to provide a hopeful treatment option for PLWH who have trouble in continuing a daily pill-based regimen. LA tissue-targeted injectable synthetic nanotherapy, which includes antibody drug-conjugates, inorganic nanoparticles, lipid vesicles, polymer/lipid nanoparticles, polymer micelles, and hydrogels/implants/suspensions, will pave a long way in clinical experiments, regardless of the potential of high bioavailability, high tissue penetration in lymphatic tissues, and long plasma half-lives.

Two-drug regimens (2DR)

There has been a renewed and increased interest in challenging traditional three-drug HIV therapies and moving toward 2DR for initial or maintenance treatment of PLWH.[4] Increasingly growing evidence has shown that dual therapy, which harbors effectiveness, may reduce medical cost and toxicity. Some guidelines recommend DTG + 3TC, darunavir/ritonavir (DRV/r) + raltegravir (RAL), in addition to DRV/r+ 3TC as the latent initial ART are recommended in particular situations, like as tenofovir or abacavir fail to be applied. DRV/r +RAL is restricted to patients with viral load (VL) <100,000 copies/mL and CD4 >200 cells/μL. The safety, tolerability, and efficacy of monthly LA injectable cabotegravir and rilpivirine (RPV) for maintenance therapy of HIV-1 infection has been established. Importantly, participants expressed greater satisfaction with injectable therapy than with the daily regimes. However, other 2DR such as DTG/RPV and a boosted protease inhibitor plus an INSTI are not recommended in the guidelines. Moreover, the efficacy of dual regimens is restricted in case of co-infection of the hepatitis B virus. Furthermore, no investigations have been conducted on the use of dual regimens in cases of tuberculosis co-infection, pregnancy, and renal disease.

Challenges of ART

Despite its enormous progress, there are numerous challenges in the implementation of ART. First, drug-induced and transmitted resistance, difficulty in adhering to daily regimens, and drug-drug interactions are some of the barriers to successful ART. Second, with the gradual

increase in life expectancies of PLWH, non-AIDS morbidity has become increasingly prominent. Integrase inhibitors, which have a safer side-effect profile than other ARV drugs, for commencing ART or those failed treatments. However, DTG and other INSTIs have been suggested to cause excessive weight gain. Further investigation of neural-tube defects and other metabolic complications associated with INSTIs is warranted.

Functional Cure

HIV can rebound quickly when ART is discontinued even after several years of effective viral suppression, owing to the presence of a sustainable reservoir of latently infected cells. Therapy is able to cure or shortly eradicate the virus, thus achieving a functional cure that a sustainable and strict immune control is obtained without medication. It is a transformative tool for a large number of PLWH.[1]

The past decade of research has resulted in a deeper understanding of the molecular and cellular mechanisms of HIV latency.[1] There have been efforts to develop cellular or gene therapy to control or clear infection and strategies to permanently silence viral genomes ("Kick and kill" regimens), induce apoptotic death in infected cells, or allow viral remission in the absence of viral eradication. In the future, research focusing on the development of curative therapy that targets and eliminates the persistent reservoirs of HIV is warranted.

Furthermore, bnAbs in combination with LA agents can help achieve long-term viral suppression without having to take daily pills. All available resources are being optimized for designing improved functional, therapeutic, and prophylactic regimens before the development of an efficient vaccine against all circulating HIV variants.

To sum up, during the past forty years, concerns about advances of ART revolutionized HIV has been in existence. Before the arrival of a cure for HIV, future research needs to be oriented with the improvement of the efficacy, securities, conveniences, as well as equitable level of ART for all of the HIV people. The current growth of novel ARV agents is required to enhance the HIV treatment cascade, which aims to upgrade PLWH's lives in the meanwhile of lowering the secondary transmission and striving to bring the HIV epidemic to the end around the world.

Conflicts of interest

None.

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How to cite this article: Bai RJ, Dai LL, Wu H. Advances and challenges in antiretroviral therapy for acquired immunodeficiency syndrome. Chin Med J 2020;133:2775–2777. doi: 10.1097/CM9.0000000000001226