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New prospects for HIV treatment

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HIV infects important cells of the immune system called CD4 cells. When these cells are destroyed by HIV disease, the immune system becomes dysfunctional and weakened and patients are at risk of other infections and even rare forms of cancer. Antiretroviral therapy (ART) aims to control HIV replication and thereby prevents the destruction of the immune system. ART has come a long way. In 1987 the first drug to treat HIV was registered. Despite the initial promise, as monotherapy, it did not achieve sustained benefit. The reason for this early failure was soon realised to be the development of drug resistance, as one drug allowed continued viral replication and evolution, with accumulation of multiple drug resistance mutations. In contrast, when triple combination therapy ART (cART) became available in 1996 and 1997 it had a remarkable success. The ability of these drug combinations to effectively suppress viral replication in the vast majority of patients has been pivotal for therapy success. When an appropriate regimen is chosen, viral loads become undetectable and viral evolution and hence the development of drug resistance is completely halted.

Despite these developments, South Africa lagged behind. Only in 2004 cART became available in the public sector, improving the lives of the now just over 7 million people living with HIV in South Africa.

There has been progress since the earliest cART regimens: Drugs have become safer, resulting in fewer immediate side effects and long term toxic effects; Regimens have also become easier to take and where early regimens often required dosing as frequently as 3 to 5 times per day, most first-line treatment regimens now comprise a single daily fixed dose combination (FDC) tablet. Safer therapies have improved the risk benefit ratio of treatment. Recent studies, the START and TEMPRANO studies showed that early cART initiated irrespective of CD4 count had health benefits compared to therapy initiated when CD4 counts dropped to below 500 cells per microliter (1,2). This combined with evidence from the HPTN052 study that treating an HIV infected partner prevents onward transmission to a negative partner (3) has resulted in WHO and South African guidelines advising initiation of ART as soon as feasible in newly diagnosed patients. Rational drug design has also contributed to the development of "robust" drugs, which require multiple mutations before they lose benefit, which are often crippling to viral replication, therefore increasing the barrier to development of drug resistance. These high genetic barrier drugs have often been used in treatment experienced patients, who had no other options. However, as some new drugs have both good tolerability and high genetic barriers there is a recent drive to include such robust drugs in first-line. One of the most promising new drugs is dolutegravir (DTG). It has limited toxicity, is tolerated by most individuals and drug resistance is exceedingly rare. As generic drug formulations are most often more affordable than the original patented formulation, once generic DTG-containing FDC regimens became available in South Africa it would likely be the primary choice for first-line therapy (4).

Importance of treatment adherence

Although therapy has become more tolerable and once daily FDC tables have made it easier to adhere to prescribed treatment, it still requires that patients take their medication regularly to achieve sustained viral suppression. When treatment adherence is inadequate and replication is therefore not suppressed, drug resistance is likely to develop, except in cases when high genetic barrier regimens are used. A novel advance that keeps drug levels high enough without the need for daily treatment is using long acting formulations that could be administered as monthly depot injections: in this respect trials combining nanoformulated cabotegravir with rilpivirine are showing early promise (5).

Irrespective of receiving daily oral or future injectable depot therapies, these require health care visits for medication and monitoring of safety and response. If patients are treated early enough, before a lot of immune system damage has occurred, life expectancy is close to normal, as long as they remain on successful treatment. However, when patients stop therapy, virus rebounds to high levels in most patients, sometimes associated with severe illness and even an increased risk of death. The aim of "cure" is to obviate the need for ongoing therapy and monitoring. ART alone cannot cure HIV as among the cells that are infected are very long-living CD4 memory cells and possibly other cells that act as long-term reservoirs. HIV can hide in these cells without being detected by the body's immune system. Therefore even when ART completely blocks subsequent rounds of infection

of cells, reservoirs that have been infected before therapy initiation persist and from these reservoirs HIV rebounds if therapy is stopped. “Cure” could either mean an eradication cure, which means to completely rid the body of reservoir virus or a functional HIV cure, where HIV may remain in reservoir cells but rebound to high levels is prevented after therapy interruption.

Achieving functional cures

Thus far, there is only one scientifically proven instance of a patient, the “Berlin patient”, Timothy Brown, who had been HIV infected and in whom HIV can no longer be detected even though he is not receiving ART. This is a very special case, and his cure was achieved after two bone marrow transplants from a donor which had blood cells that are resistant to his HIV infection, as they lacked CXCR5 receptors (6). A bone marrow transplant is a very risky procedure and was only attempted as this patient required it for leukaemia. It is also often challenging to find a matching donor and much more difficult to find one that also has this genetic polymorphism, called the CCR5 delta 32 deletion. Moreover, Timothy Brown almost died due to complications of the transplants and this approach to cure has never been replicated in other patients. The “Berlin approach” therefore does not provide a scalable cure. Attempts to mimic the “Berlin patient” cure by changing CD4 cells through gene therapy to make them resistant to HIV without the need for a high risk bone marrow transplant are in early stages of investigation, and it will have to be seen if this would work. It is also debated whether the Berlin patient cure is a true eradication cure as very low levels of virus may still be present in reservoirs in his body although HIV assays cannot detect it and his strain of HIV cannot reproduce in his resistant cells. Another approach, which attempts to eradicate HIV from reservoirs is the so-called “shock and kill” approach. This aims to induce HIV replication in reservoir cells by using latency reversing agents (LRAs) to stimulate these cells to produce virus so that infected cells can be recognised and killed by the immune system, or alternatively through administering immune effectors (antibodies or immune cells that target and kill virus infected cells). “Shock and kill” has met with challenges: LRAs achieve a low rate of reservoir cell induction (stimulate them to produce viral protein), in patients infected for long before treatment, there is a poor ability to kill infected cells and viruses that had been archived in reservoirs often represent strains that had mutated such that they are no longer recognisable by the individual’s immune responses.

In contrast, a much simpler approach has shown promise in achieving functional cures. This is based on early ART. Whereas less than 1% of individuals naturally control HIV replication, after early therapy for a few months followed by interruption as many as 15% in the Visconti study and even more African patients in the SPARTAC trial showed post therapy control (7,8). However, as the symptoms of early HIV infection are not specific, it is difficult to diagnose early and it requires special sensitive tests that could detect HIV virus before the body mounts an antibody response. Implementing early sensitive testing on a large scale would require novel innovations, as the current most sensitive tests are costly and not freely available. When early therapy is combined with an effective adjunctive vaccine, or other immune-based therapies, the proportion of patients who achieve functional cures would probably increase. Such studies combining early therapy with therapeutic vaccination are in early stages or are being planned. One very interesting and surprising finding, investigated in rhesus monkeys, is the combination of very early therapy with vedoluzimab, an antibody used to treat inflammatory bowel disease. This antibody binds to receptors on CD4 cells that affect their homing to the gut. It was found that when a monkey version of this antibody is given in combination with early therapy shortly after infecting these monkeys, they could control simian immunodeficiency virus (SIV), which is similar to HIV, even after therapy was stopped. Although the mechanism of this approach to a functional cure is not yet fully understood, following on these promising results in monkeys, the first human trials in HIV infected individuals have been planned. Time will tell if this approach or other attempts to achieve a functional cure works in humans. Considering the high number of patients currently infected in Southern Africa, research into functional cures is a priority. An effective functional cure would render an HIV infected patient in “remission”, either no longer needing to visit health care facilities or needing far less frequent care, improving their quality of life and lessening the financial burden of HIV disease on society. Patients who achieve a functional cure may also be non-infectious which may prevent onward transmission.

Prevention has the highest priority

Of all HIV interventions, preventing new infections should remain the highest priority. Behavioural interventions have shown varied success and approaches such as circumcision provide only partial protection. Despite some indication that a particular vaccine, RV144, may reduce the risk of infection in the short run, an effective vaccine is not yet available. A potentially promising vaccine study, the HVTN 702 study has just commenced with results only expected in 2020 (9). Treating HIV infected individuals early has been shown to be one of the most effective ways of preventing

sexual transmission of HIV. Similarly the use of cART in pregnant and breastfeeding women has dramatically reduced transmission to their babies. When managing high risk individuals, provision of antiretrovirals for pre-exposure prophylaxis (PreP) is now recommended as it could be very effective in patients who adhere to their prescription. However, inadequate adherence has limited the success of any PreP trials. There is therefore excitement about the use of long acting injectable ART formulations, which may result in sustained protective levels and thereby improve the efficacy of these prevention efforts (10).

In summary, recent advances in ART have improved the success of treating infected individuals and have provided valuable tools to prevent infection. Early ART also offers one of the most practicable components in attempting to achieve functional cures, but diagnosing and treating HIV early remains a challenge.

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