

Current challenges in the treatment of HIV

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KEY WORDS

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ABSTRACT

In this review of the current challenges in the fight against HIV, we describe the state of the HIV epidemic and the framework put in place using the 90-90-90 objectives to try and curb the epidemic worldwide. There are numerous effective and evidence-based prevention measures against the spread of HIV, but the biggest challenges lie in the lack of political commitment, reluctance to address issues of sexuality and reproduction, and criminalization of key populations that are at the highest risk of HIV. Access to HIV treatment and continued care without stigmatization should be as easy and cheap as possible for those who are tested and diagnosed with HIV to achieve the best results worldwide. Regarding the treatment of HIV, the last decades have been very successful in dramatically improving the quality of life of people living with HIV, reducing the transmission rate and decreasing HIV-associated morbidity and mortality. It could even be argued that the next milestone will be a strategy that allows individuals to stop combination antiretroviral therapy safely before a cure is discovered. Despite great progress, people with HIV have shorter life expectancy than those without the virus, and the underlying causes are probably multifactorial, including premature aging, drug toxicities, and comorbidities. Even if challenges remain, hope should too, with the ultimate goal to end the HIV epidemic.

Introduction In June 1981, the Centers for Disease Control and Prevention reported the first cases of acquired immunodeficiency syndrome (AIDS).¹ They soon turned out to be sentinel cases of a worldwide epidemic caused by a retrovirus called human immunodeficiency virus (HIV). The impact of the epidemic on global health has been huge. Over the past 40 years, 77.3 million people have become infected with HIV and 35.4 million people have died from AIDS-related illnesses.² Fortunately, the devastating spread of the virus was counterbalanced by actions from different communities, ranging from patient groups to scientific research teams, each contributing within its own domain of expertise. There is indisputable evidence that the global response against HIV was a success in the last 2 decades.³ In 2017, less than 1 million people worldwide died of AIDS-related causes, which is the lowest number recorded this century.

A major determinant of reduced mortality rates in people with HIV infection is a sustained access to combination antiretroviral therapy (cART). Early initiation of cART and suppression of plasma viral load (pVL) reduces mortality and HIV transmission rates and improves the quality of life.³

At the 2014 International AIDS Conference in Melbourne, the Joint United Nations Program on HIV/AIDS (UNAIDS) proposed the 90-90-90 and 95-95-95 targets to accelerate efforts towards ending the AIDS epidemic as a public health threat by 2030.^{4,5} The aim of this test-and-treat model is that by 2020 and 2030, respectively, at least 90% and 95% of all people living with HIV should be diagnosed, at least 90% and 95% of those diagnosed should be on cART, and at least 90% and 95% of those on cART should be virologically suppressed.

Although the progress made so far is encouraging, HIV epidemic is far from over. According to a systematic analysis of national HIV treatment cascades from 69 countries, none of the countries had met the 90-90-90 targets.⁶ Diagnosis (first target, 90% of all people with HIV diagnosed) ranged from 87% in the Netherlands to 11% in Yemen; treatment coverage (second target, 81% of all diagnosed people started on cART) ranged from 71% in Switzerland to 3% in Afghanistan; and viral suppression (third target, 73% of all people on cART virally suppressed) was between 68% in Switzerland and 7% in China. Moreover, the success in saving lives has not been matched with equal success in reducing new

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HIV infections. About 1.8 million people became newly infected with HIV in 2017.² New infections continue to fuel the epidemic, and underscore the long-term need for antiretroviral treatment, which is inevitably linked with increasing costs. Furthermore, although HIV is recognized as a virus that can affect any of us, stigma persists and people living with HIV experience continued discrimination.

It is thus clear that the battle against HIV is far from over. In this article, we will focus on the major challenges that need to be addressed to close the gaps in prevention, diagnosis, treatment, and care of HIV infection to end the epidemic by 2030.

Challenge 1: prevention of new HIV infections Overriding challenges have emerged in HIV prevention and care in the last few years. They include societal and psychosocial determinants of health such as poor social support, gender-based violence, mental health issues, stigma, discrimination, food insecurity, and poverty. Having an impact on those determinants is especially critical for women, who are among those most vulnerable to HIV.⁷ It has been shown that gender inequality and poverty, aggravated by intimate partner violence, increase the vulnerability of heterosexual women to HIV.⁸ More generally, a strong association has been found between HIV-related stigma and the following: depression, social support, adherence to cART, and access to and use of health and social services.⁹ Therefore, prevention programs all over the world must include interventions that target gender inequality and economic issues.

Another challenge is the appropriate tailoring of prevention interventions to the type of HIV epidemic at hand in a given country or region. In concentrated or mixed epidemics, where certain risk groups or key populations are disproportionately affected by the HIV epidemic (such as sex workers, men who have sex with men [MSM], long-distance truck drivers), the following types of interventions have been shown to be effective: behavior change communication; condom promotion; sexual health and harm-reduction services such as needle exchange programs¹⁰ and opioid substitution therapy¹¹; HIV testing, counseling, and treatment^{12,13}; solidarity and community empowerment; and supportive local and national legal and policy environments.

Preexposure prophylaxis (PrEP) is the latest prevention tool. It has been recommended by the World Health Organization since 2015 for various groups at high risk for acquiring HIV. Studies on PrEP efficacy among serodiscordant couples, heterosexual men, women, MSM, intravenous drug users, and transgender women have accumulated over recent years and showed that the treatment is effective when adherence is high. In studies of PrEP in the population of MSM, HIV incidence dropped by up to 86% in fully adherent very high-risk MSM who used PrEP.¹⁴ In a study

of PrEP in intravenous drug users, a 49% reduction of HIV incidence was very promising.¹⁵ In sex workers, however, high adherence rates were more difficult to reach because of mobility issues and education levels.

In areas of generalized epidemics, studies have found that the most effective measures to reduce HIV incidence are treatment as prevention (TasP) and voluntary male medical circumcision (VMMC). Some studies demonstrated that financial incentives are effective as well, probably because of an improvement in living conditions and less pressure to exchange sex for money or food.¹⁶

TasP reduced the risk of HIV acquisition by at least 96% in a study setting of serodiscordant couples where most new infections did not come from the official partner.¹² Even if that number might be lower in real-life settings, if patients adhere to antiretroviral therapy (ART), the risk of transmission to others is considered to be near 0 in the absence of intercurrent sexually transmissible diseases. The World Health Organization has therefore changed its recommendation and stated that every person diagnosed with HIV should be treated immediately, independently of CD4 cell count or clinical presentation. Prevention of mother-to-child transmission by treating the mother could be seen as part of the TasP strategy, where TasP is complemented by specific guidelines for the treatment of the newborn and local guidelines on breastfeeding, depending on the country.

VMMC is another very effective tool to reduce HIV incidence in generalized epidemics. Studies first showed a 60% protective effect in clinical trials.^{17,18} Longer-term effects might even be as high as 76% protection after 3 years.^{19,20} The individual benefit of VMMC is important, but the challenge also lies in performing enough voluntary circumcisions on a large enough scale to significantly affect the epidemic. The UNAIDS targets for VMMC were not met in 2016.

Despite the knowledge on the best interventions for particular settings and the progress made in scaling up ART in many countries, the global incidence of new HIV infections is not decreasing at a sufficient rate. The UNAIDS suggests 3 interconnected reasons to explain this: lack of political commitment and therefore inadequate investments; reluctance to address issues of sexuality and reproduction, especially related to young people and key populations, as well as reluctance to address harm reduction; and lack of systematic prevention implementation.²¹ Eastern Europe and Central Asia are often taken as examples of areas where some of these issues desperately need to be addressed, because the incidence of HIV increases in those regions whereas a decrease is observed in the rest of the world.²²

The UNAIDS seeks to boost the leadership and accountability for HIV prevention on global and national levels and to fast-track the implementation of effective HIV prevention programs at national levels by providing guidance

on effective approaches to achieve the prevention targets of the 2016 United Nations political declaration on HIV and AIDS. These include ensuring access to combination prevention options with detailed goals by 2020.

Challenge 2: diagnosis and access to care Access to care should be cheap and nondiscriminating worldwide at any step of the cascade to achieve the 90-90-90 goals set by the UNAIDS. A massive progress has been made over recent years to achieve better diagnosis, treatment, and viral undetectability. Unfortunately, similar hurdles as those described in the previous section regarding prevention services lie in the way of universal HIV testing and access to care. To name only a few: poverty, stigma (related to HIV itself or to psychoactive substance abuse), gender inequalities, and gender-based violence all over the world.⁷⁻⁹

The first step of the cascade is the diagnosis of new HIV infections. If the goal established in the first step of the cascade is not reached, the goals from the following 2 steps will not follow suit. Many regions of the world have been very successful in achieving high numbers of diagnosed HIV-positive individuals. However, across sub-Saharan Africa, the most recent UNAIDS report estimated the number of HIV-positive people that are aware of their HIV status at only 45%. Proactive testing such as auto-tests or door-to-door testing, instead of passive testing where people come and test voluntarily, could be the answer. Also, multidisease health campaigns have shown promising results in Kenya and Uganda, but need strong community involvement and logistics.^{23,24}

The next steps of the cascade are treatment and retention in care to reach an undetectable viral load in the long term. To achieve these steps, the health systems, especially those with low service coverage, need to make a more general progress. The practical, but vital aspects of treatment delivery and the challenges around costs also remain pertinent. The drugs have to be free, and stocks have to be managed without breaks in the delivery of antiretroviral drugs. The treatment guidelines regarding second- and third-line treatments may also have to be reviewed in some regions to offer easier and cheaper treatment options. Many countries reached, and many others are within the reach of, the goals set in the second and third steps of the cascade, while others need the continuous work of the local and national political leadership on these issues.

As mentioned above, the most vulnerable groups are key populations that are often left behind at all stages of the HIV cascade. Indeed, while the HIV prevalence in some of these groups is the highest, they are often the groups who benefit the least from the HIV testing and treatment facilities.^{4,25-29} Health systems can become discouraging and even hostile to these patients

because of stigma and discrimination within the systems.³⁰ This is not surprising in countries where national laws clearly exclude some of those populations through criminalization of sex work and drug abuse. For example, around 78 countries still criminalize same-sex sexual behavior.⁴ Maybe as a consequence, in key populations in Asia for instance, less than half of the individuals in those high-risk groups were aware of their HIV status in 2012.³¹ Moreover, a clear link was observed between criminalization laws and the inability to implement evidence-based medical interventions, such as opioid substitution programs or community empowerment of MSM or sex workers.

Generally, removing policies and laws that have a negative impact on testing and treatment of HIV seems essential. They include laws against HIV-positive individuals, regulations around HIV nondisclosure, and laws discriminating against specific risk groups. It could even be argued that key populations deserve prioritized responses based on human rights, as supported by UNAIDS.³¹ It has been projected that decriminalization of, for instance, sex work could decrease the incidence of HIV amongst sex workers by 33% to 46% over 1 decade overall.³²

Reaching the 90-90-90 targets of the cascade for children and adolescents is another major challenge, especially in areas of generalized epidemics. Even children born to HIV-positive mothers are not tested on a large enough scale. Treatment regimens have long been more complicated for children than for adults, while adherence can be even more challenging in young people.³³⁻³⁵

Challenge 3: treatment of HIV Three milestones have been achieved in the field of ART over the last 2 decades, or at least in part: a dramatic decrease in HIV-associated morbidity and mortality rates, a reduction in the transmission rate of HIV, and an improved quality of life of people living with HIV.³⁶

The first milestone was on December 6, 1995, when saquinavir, the first protease inhibitor, was approved by the US Food and Drug Administration for use in combination with nucleoside analogues.³⁷ This initiated the era of highly active ART, nowadays known as cART. This era was characterized by a dramatic decrease in HIV-related morbidity and mortality rates.³⁸⁻⁴²

The second milestone was the introduction of the strategy of TasP. This refers to the use of cART in serodifferent heterosexual and homosexual couples to maximally reduce pVL and to consequentially reduce the risk of transmission of HIV to the uninfected partner.^{12,43-46} Further proof that cART impedes HIV transmission was provided by the fact that the risk of mother-to-child transmission is directly linked to maternal pVL.⁴⁷ TasP is now considered a key element of HIV prevention and a major part of the solution to ending the HIV epidemic.⁴⁸

The third and most recent milestone was the insight that was gained from 2 large randomized controlled trials, START (Strategic Timing of Antiretroviral Therapy) and TEMPRANO (Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa), both of which addressed the issue of the optimal time to initiate cART. These trials demonstrated a reduction of approximately 50% in morbidity and mortality rates among HIV-infected individuals who initiated cART at CD4⁺ T-cell counts of more than 500/mm³ compared with individuals starting therapy at CD4⁺ T-cell counts below 350/mm³.^{49,50} Based on these data, all major treatment guidelines now recommend cART for all HIV-infected individuals, regardless of their CD4⁺ T-cell counts. This is also known as the test-and-treat strategy.⁵¹⁻⁵³ The current recommendation has been partially facilitated by optimized drug profiles that maximize long-term tolerability and safety as well as regimen simplification through the combination of 3 active drugs into single-tablet regimens.⁵⁴ Nevertheless, cART is still unable to eradicate HIV infection and thus needs to be taken for the rest of an individual's life. As an estimated 22 million of people with HIV still have no access to ART and as new infections are continuously fueling the number of additional people in whom cART needs to be initiated, raising global HIV/AIDS resources and funding is urgently needed to ensure universal cART coverage.⁵⁵

Elaborating on the need for lifelong cART, the next milestone to be reached in the field of HIV treatment should be a strategy that allows individuals to stop cART safely.

Timothy Brown is known as the first and, so far, the only HIV-infected individual in whom a "true cure" or "sterilizing cure" has been reported following a treatment including transplantation of hematopoietic stem cells from a donor with CC chemokine receptor 5 (CCR5)Δ32 mutation in the context of acute myeloid leukemia.⁵⁶ Unfortunately, in the 9 years following Brown's report, no other cures for HIV have been achieved. At least another 6 patients with hematologic malignancy have received a graft from a donor homozygous for CCR5Δ32, but none of them survived for longer than 1 year due to relapse of malignancy or graft complications.^{57,58} Moreover, in one of the individuals, the virus rebounded as a CXCR4-tropic strain. Furthermore, the mortality rate associated with hematopoietic stem cell transplantation precludes its use as a cure for people with HIV without an accepted clinical indication for transplantation.⁵⁹

The most significant barrier to complete eradication or cure of HIV infection is the establishment of a latent HIV reservoir within days of HIV acquisition and in multiple T-cell subsets.⁶⁰ This reservoir is defined as replication-competent intact virus integrated into the host genome in the absence of virus production.⁵⁹ As initiation of cART very early after HIV acquisition is known to reduce the size of the viral reservoir and to

improve the quality of the HIV-specific CD8⁺ T-cell responses, several studies have investigated a cure for HIV in individuals who started cART very early after HIV infection.^{59,61} Indeed, some individuals, known as posttreatment controllers (PTCs), have shown to maintain pVL suppression in the long term after cessation of ART.⁶²⁻⁶⁴ To date, the VISCONTI trial (Viro-Immunologic Sustained Control After Treatment Interruption) is the best-characterized cohort of PTCs. Although posttreatment control is most common after ART administration during acute infection, it has also been described in individuals treated during chronic infections and in ART-naïve patients.^{64,65} The true incidence of posttreatment control has not yet been established but in a post hoc analysis of a prospective trial of individuals with primary HIV infection, transient virological control was achieved in 15.1% of participants who were assigned to receive early ART and 7.9% of those assigned to receive no ART.⁶⁴ Unfortunately, in most patients, interruption of cART that was started very early is still associated with viral rebound and therefore insufficient to cure HIV infection.⁶⁶⁻⁶⁸

Rather than achieving a sterilizing cure, meaning that HIV is eliminated from all infected cells, a strategy to obtain a functional cure where HIV remains durably suppressed in the absence of cART is likely to be found first. As reviewed by Pitman et al,⁵⁹ experimental strategies that are currently being explored include strategies targeting the HIV replication cycle (such as gene therapy and latency reversal agents), strategies enhancing the HIV-specific immune responses (such as T-cell vaccines and broadly neutralizing antibodies), and strategies modulating the immune response (such as immune checkpoint inhibitors and anti-inflammatory drugs). Although a combined approach will most likely be needed, the safety of each individual intervention should be well established because people with HIV nowadays have a near-normal life expectancy, which makes toxicity less acceptable than for other life-threatening diseases.

Another important issue is safety and tolerability of antiretroviral drugs. Because cART currently enables prolonged virologic suppression, improved clinical outcomes, and longer survival, people with HIV are exposed to antiretroviral drugs for decades. Thus, further simplification of antiretroviral regimens should be the focus of future clinical development. At least two 2-drug single-tablet regimens (dolutegravir plus rilpivirine and dolutegravir plus lamivudine) are currently challenging the paradigm of combining 2 nucleoside reverse transcriptase inhibitors with a third agent. In May 2018, the European Medicines Agency granted marketing authorization for Juluca®, the first fixed-dose 2-drug regimen, containing dolutegravir and rilpivirine, for the treatment of HIV infection in adults who are virologically suppressed on a stable antiretroviral regimen for at least 6 months with no history of virological

failure and no known or suspected resistance to any nonnucleoside reverse transcriptase inhibitor or integrase strand transfer inhibitor.⁶⁹ A report of the 48-week results from the phase 3 GEMINI trial (Efficacy, Safety, and Tolerability Study Comparing Dolutegravir Plus Lamivudine with Dolutegravir Plus Tenofovir/Emtricitabine in Treatment-Naïve HIV-infected Subjects) by Cahn et al,⁷⁰ presented during the 22nd International AIDS Conference in July 2018, demonstrated a noninferior efficacy of dolutegravir plus lamivudine to dolutegravir plus tenofovir/emtricitabine in treatment-naïve adults with HIV. More drug-related adverse events were reported in the dolutegravir plus tenofovir/emtricitabine arm. The ongoing TANGO trial (Switch Study to Evaluate Dolutegravir Plus Lamivudine in Virologically Suppressed HIV Type 1 Positive Adults) is designed to demonstrate noninferiority of switching to dolutegravir and lamivudine as compared with continuing a tenofovir alafenamide-based regimen over 48 weeks in virologically suppressed subjects. By analogy, the safety and efficacy of cabotegravir and rilpivirine as 2-drug oral maintenance therapy has been evaluated in the phase 2b LATTE trial (Long-acting Intramuscular Cabotegravir and Rilpivirine in Adults With HIV-1 Infection).^{71,72} The data obtained should guide future studies in which the long-acting formulations of both cabotegravir and rilpivirine will be used for treatment of HIV infection.

Treatment simplifications with long-acting injectable formulations of drugs with established oral efficacy, such as cabotegravir and rilpivirine, will also be assessed in the near future in the POLAR study (Study to Assess Antiviral Activity and Safety of Long-acting Cabotegravir Plus Long-acting Rilpivirine, Administered Every 2 Months, in HIV-Positive Subjects From the LATTE Study). If proven to possess long-term safety and efficacy, long-acting injectables could provide additional options for a simplified and potentially more convenient maintenance therapy. However, long-term sustainability and tolerability of monthly or bimonthly intramuscular injections need to be established. Other sustained-release drug delivery technologies could possibly increase the convenience of ART, but these may require more potent drugs due to the limited drug delivery capacity of patches, implants, and other currently available technologies.

Two-drug regimens may also reduce the cost of lifelong cART, which is crucial in resource-limiting settings. They may have improved long-term tolerability by minimizing the cumulative drug exposure and reducing drug-to-drug interactions, which is especially important in aging patients with comorbid conditions. But it is still unclear how the 2-drug regimen approach will stack up against the firmly established norm of a 3-drug regimen. We need to ensure their long-term efficacy beyond the 48 weeks data, comparable with that of a conventional 3-drug regimen. In addition to viral suppression in patients, 2-drug regimens

will also have to prove efficient in terms of TasP and prevention of mother-to-child transmission, and in reducing HIV-related immune activation and inflammation, thought to contribute to end-organ damage.⁵⁴

Challenge 4: comorbidities and aging One of the main beneficial effects of cART is increased longevity. Indeed, people with HIV who have access to treatment live longer. Half of the patients living with HIV in high-income countries are now aged 50 years or older.⁷³ European HIV surveillance data also indicate that a larger proportion of HIV diagnoses are being made in older people. Those aged over 50 years at HIV diagnosis comprised 13% of all diagnoses in 2007 globally, rising to 19% of all diagnoses in 2016.⁷⁴

However, a gap remains between the life expectancy of people with HIV and that of the general population. This gap has become a focus of research. It has been hypothesized that a state of persistent immune activation and heightened inflammation, despite stable suppression of viral replication, increases the risk of comorbidities, in particular cardiovascular disease and non-AIDS cancers.^{75,76} Besides, aging itself is associated with comorbidity, including in elderly HIV-infected patients who are considered to be prone to accelerated aging as well.^{77,78} Coinfection with other microorganisms, such as hepatitis B or hepatitis C virus, can also contribute to an increase in morbidity and mortality rates on top of the HIV infection.⁷⁹ And, last but not least, lifestyle-associated risk factors, such as obesity, smoking, and alcohol and substance abuse are more prevalent among HIV-positive people.^{36,76} As an illustration of these multiple factors, a Belgian multicenter retrospective study of 5787 HIV-positive patients characterized its population in relation to noninfectious comorbidities (diabetes mellitus, cardiovascular events, chronic kidney disease, arterial hypertension, Hodgkin lymphoma, anal cancer, lung cancer, and liver cancer) and found an 8.9% rate of polyopathy (ie, the concomitant diagnosis of more than 1 of these comorbidities) for all ages, rising to 24.5% for the age group above 60 years.⁸⁰

In addition, the potential toxic effects of long-term ART must be considered when studying comorbidities linked with HIV. In a multicenter study of 600 patients who initiated ART between January 2007 and June 2010, toxicity of the therapeutic regimen (including disorders of kidney, liver, metabolism, gastrointestinal system, central nervous system, and skin) was the main reason for treatment discontinuation in 49% of patients.^{81,82} Chronic or long-term toxicity resulting from the cumulative effect of sustained exposure can be particularly difficult to manage as it can be masked by or mingled with other comorbidities. In addition, long-term toxicity can manifest itself months or years after initial exposure.⁸² Typical examples are the metabolic toxicity of (mainly older) protease inhibitors (resulting

in dyslipidemia, insulin resistance, and diabetes mellitus) and the involvement of tenofovir in the pathogenesis of renal impairment and bone loss (reflected by osteopenia and osteoporosis).

Medical management of HIV-infected patients has become increasingly complex. The focus shifted from getting the viral replication under control and halting the progression of immune deficiencies towards prevention and treatment of chronic health problems in people with quasi-normal life expectancies. Again, these chronic conditions may be cardiovascular diseases, such as ischemic strokes, diabetes mellitus, dyslipidemia, and chronic kidney dysfunction, neurocognitive impairment, osteoporosis, cancer, and frailty.⁸³

As a result, the package of care offered to HIV-positive patients should start with a careful evaluation of a person's general health state, with attention to lifestyle, concomitant diseases and their treatments, and age-related comorbidities. A comprehensive and individually tailored plan should be outlined, and it is important to realize that its practical implementation can benefit from a multidisciplinary approach. The ultimate goal of therapy is to help the HIV-infected person to live in conditions of optimal health, with mitigation of treatment toxicities and of potential comorbidities.

Conclusions An enormous progress has been achieved worldwide regarding the management of HIV, such that ART has turned HIV infection into a medically manageable chronic condition. However, the future is brighter only for those who have access to treatment. Indeed, many hurdles remain.

First, targeting key populations, that is, those who are most vulnerable to HIV, is not easy due to social, economic, and political factors in some regions of the world. This is true for prevention of new HIV infections and all the steps of the 90-90-90 cascade. Secondly, each step of the 90-90-90 cascade is associated with specific challenges: getting people tested and diagnosed, treating everyone immediately, and keeping patients under care. Thirdly, issues around the best possible choice and efficacy of ART and possible toxicities of ART are not to be underestimated. Lastly, comorbidities associated with HIV must not be forgotten. People infected with HIV are getting older without doubt, but the state of chronic immune activation due to the presence of the virus adds to this. A sterilizing cure would be the ultimate victory but is not yet in reach.

However, raising awareness and being reminded of the successes that have been accomplished since the discovery of HIV should be a driving force for dealing with those obstacles. With one ultimate goal in mind: ending the HIV epidemic once and for all.

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