HIV

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The benefits of combination antiretroviral therapy (cART) for HIV replication and transmission control have led to its universal recommendation. Many people living with HIV are, however, still undiagnosed or diagnosed late, especially in sub-Saharan Africa, where the HIV disease burden is highest. Further expansion in HIV treatment options, incorporating women-centred approaches, is essential to make individualised care a reality. With a longer life expectancy than before, people living with HIV are at an increased risk of developing non-AIDS comorbidities, such as cardiovascular diseases and cancers. Antiretroviral strategies are evolving towards a decrease in drug burden, and some two-drug combinations have proven efficacy for maintenance therapy. Investigational immune checkpoint inhibitors and broadly neutralising antibodies with effector functions have energised the HIV cure research field as the search for an effective vaccine continues. In this Seminar, we review advances and challenges relating to the goal of an AIDS-free world.

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Introduction

The HIV field has been through three major therapeutic revolutions since the virus was first isolated in 1983. The first revolution was the introduction of protease inhibitors in 1996, which, in combination with two nucleoside-analogue reverse-transcriptase inhibitors, produced highly active antiretroviral therapy (HAART) and greatly improved the prognosis of an otherwise uniformly lethal disease.[1] The second revolution, the use of treatment as prevention, was built on the promising results from observational studies,[2–5] and culminated with the HPTN 052 study.[6,7] This landmark randomised clinical trial supported the benefits of combination antiretroviral therapy (cART) in serodiscordant couples (ie, one HIV seronegative and one HIV seropositive partner) with a substantial reduction (96%) in the risk of sexual transmission of HIV when the seropositive partner had undetectable plasma HIV RNA.[6,7] In this study, no HIV transmission occurred when the HIV-infected partner was virologically suppressed. Overall, control of systemic viral replication through cART is now clearly recognised as one of the most effective ways to prevent HIV transmission.[4,7] The third revolution occurred with the first studies to show the significant individual clinical benefit of early cART, even with a CD4 count greater than 500 cells per µL.[8] Indeed, 25 years after isolating the virus, it was recognised that the deleterious effects of HIV begin within days of infection and lead to increased risk of mortality and adverse clinical events before the onset of major immune suppression.[8,9] Given unequivocal evidence that the suppression of viral replication controls disease progression and human transmission, all major treatment guidelines now recommend cART for HIV-infected individuals, regardless of their CD4 cell count, which is known as the test and treat strategy.[10–12] Meanwhile, to accelerate the end of the AIDS epidemic, UNAIDS has launched the 90-90-90 strategy, with the goals that by 2020, 90% of people living with HIV will know their HIV status, 90% of all people diagnosed with HIV infection will receive sustained cART, and 90% of all people receiving cART will have viral suppression.[13] These ambitious goals are based on a global test and treat model, as supported by mathematical modelling of the effect of universal voluntary HIV testing plus immediate cART on the elimination of HIV transmission.[14] At the same time, treatment strategies are moving towards improved individualisation and a reduced number of drugs, enabled by improvements in antiretroviral drugs, including the introduction of some long-acting formulations.

The role of psychosocial determinants of health, such as poverty, food insecurity, stigma, discrimination, poor social support, gender-based violence, and mental health (eg, depression, alcohol dependence, and neurocognitive disorders), in the HIV epidemic has become increasingly apparent, particularly for women.[15] HIV-related stigma is strongly associated with depression, social support, adherence to cART, and access to and use of health and social services.[16] Additionally, there is consistent evidence that intimate partner violence, an epidemic concurrent with HIV, is one of the major contributors to HIV vulnerability in heterosexual women, and is in turn driven by poverty and gender inequality.[17] Therefore, a combination of economic and gender transformative interventions for women and girls might be effective in

Search strategy and selection criteria

We searched PubMed for publications in English, using the terms "HIV" or "AIDS" in combination with one of the following keywords: "epidemiology", "prevention", "screening", "resource-limited settings", "pathogenesis", "reservoirs", "latency", "cure", "vaccine", "antiretroviral therapy", "toxicity", "resistance", "social determinants", "gender-based violence", and "sexual health". We focused on clinical trials, large meta-analyses, and review articles published after 2016, but we did not exclude major contributions published before then. We referenced articles that we judged to be relevant for this Seminar. We also referenced abstracts presented at two international conferences (the Conference on Retroviruses and Opportunistic Infections held in February, 2017, and the International AIDS Society Conference on HIV Science held in July, 2017).

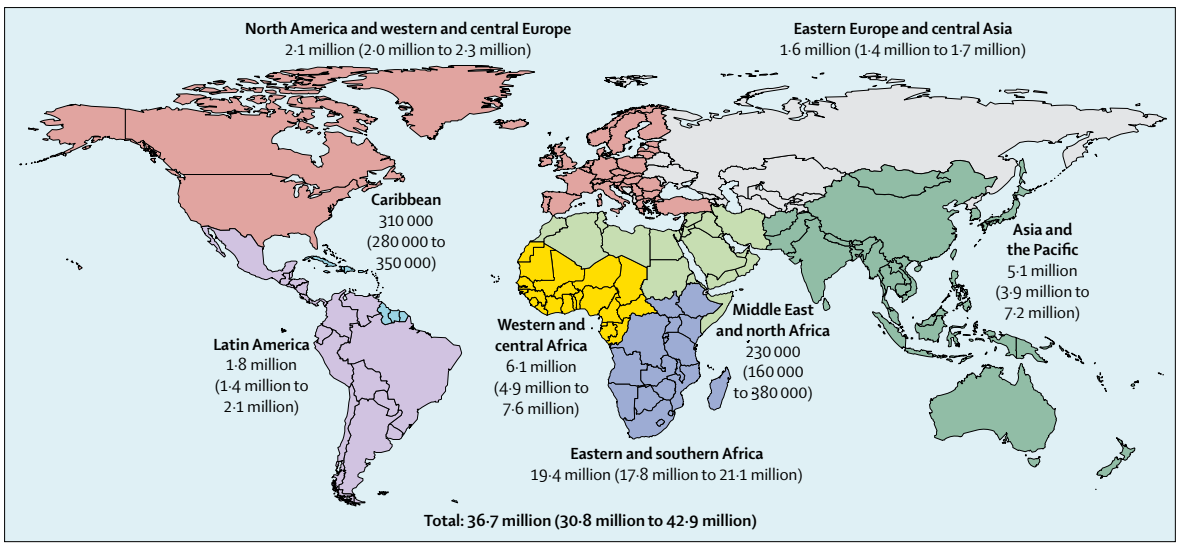

Figure 1: **Adults and children estimated to be living with HIV in 2016**
Data source: UNAIDS.[19]

reducing risk behaviours that contribute to HIV transmission and intimate partner violence.[18] Targeted interventions should address social, structural, mental, and emotional needs in HIV prevention and treatment programmes.

The two major drawbacks that have defied the tremendous therapeutic and public health achievements to date are linked to the ability of the virus to integrate into the host genome and escape the strongest immune defences. Consequently, the best antiretroviral drugs cannot eradicate HIV, which persists indefinitely in latent viral reservoirs, ready to rebound in the case of cART interruption. Second, no effective HIV vaccine is available for routine clinical use, despite progress in the understanding of immune responses against HIV. In this Seminar, we recent advances and challenges in the way to an AIDS-free world.

Global disease burden

An evolving epidemic

In 2016, an estimated 36·7 million individuals were living with HIV worldwide, of whom 51% were women, and the highest burden was in eastern and southern Africa (figure 1).[13] In the same year, an estimated 1·8 million new HIV infections occurred, representing an 11% decrease since 2010, while one million individuals died from an AIDS-related cause, a 48% decrease compared with 2005.[13] The population-specific risks of infection differ according to local HIV prevalence. Specifically, in high-prevalence countries (ie, those in eastern and southern Africa), young women tend to have the highest risk of HIV infection. Conversely, in lower-prevalence settings, other key populations (men who have sex with men [MSM], transgender people, intravenous drug users, and sex workers) have the highest risk of HIV infection.[13] The global scale-up of cART access, driven by the ambition to reach the 90-90-90 targets, has yielded remarkable progress. Indeed, in 2016, 70% of people living with HIV knew their status, 77% who knew their HIV status were on cART, and 82% of those on cART were virologically suppressed.[13] Further, a major milestone was reached in 2016 when the number of ART recipients reached over 50% of people living with HIV.[13] Some disparities are, however, alarming, such as the markedly increasing number of new infections in eastern Europe and central Asia (60% increase between 1990 and 2016) at a time when this number is sustainably decreasing in many countries.[13]

Universal testing as the gateway to HIV control

Although each component of the 90-90-90 target is essential, the first target, 90% of all people living with HIV knowing their HIV status, is arguably the most important, since it is essential to meeting the other targets. People living with HIV who are unaware of their HIV status cannot benefit from treatment as prevention, hence they constitute the hidden epidemic that is responsible for new infections.[20] Such people are also prone to late HIV diagnosis and delayed initiation of cART, which are risk factors for poor CD4 cell recovery, comorbidities, and treatment failure. Unfortunately, not enough progress has been made in solving these problems. Across 85 countries that reported real-life data to UNAIDS 29% of newly diagnosed individuals had a CD4 cell count below 200 cells per µl,[13] and the median CD4 cell count at initiation of cART is still below 350 cells per µl globally.[21,22]

HIV testing is usually done with fourth-generation enzyme immunoassays that detect antibodies and p24 antigen, or rapid third-generation enzyme immunoassays that detect antibodies only. In the past 5 years, rapid tests that are specifically labelled and packaged for self-testing have also been commercialised but their use is limited by cost. One major shortcoming of rapid HIV

tests is their inability to identify HIV infection in the acute phase before sufficient production of antibodies.[23] Thus, rapid HIV tests are acceptable in some high-prevalence settings (ie, where national or subnational prevalence is >5%), but fourth generation assays should be preferred in high-incidence groups, such as MSM engaging in high-risk sexual behaviour, to avoid missing acute infections. The promotion of HIV testing is paramount to curb the epidemic and should use new technologies and innovative service strategies, such as a smartphone dongle for HIV diagnosis at the point of care,[24] offering door-to-door HIV testing,[25] community-based counselling and testing using rapid tests for HIV,[26] self-testing, peer counsellors, and assisted partner notification, among other test and treat strategies. Routine HIV testing in centres offering comprehensive health services (such as clinics for tuberculosis and sexually transmitted diseases) is also warranted to help bridge the gap to meet WHO's first 90-90-90 target. Long-standing barriers to HIV testing in the most affected countries and populations, such as stigma and even criminalisation of sexual and gender minorities, also need to be dismantled to realise the first UNAIDS target. Punitive law enforcement practices and policies that criminalise HIV transmission, non-disclosure, and exposure to HIV are insufficient as they do not account for the stigma, violence, disempowerment, fears of abandonment, and other rights violations of women living with HIV.[15]

The second and third 90-90-90 targets are essential for improving the health of people living with HIV and for reducing the risk of sexual transmission. Indeed, if the hidden epidemic accounts for most new infections, it should not be forgotten that untreated HIV is also responsible for new infections. Access to care and antiretroviral drugs, however, differs between countries[20,27,28] and remains a major issue in some, such as in eastern Europe and central Asia, where only 27% of people living with HIV have access to cART.[13] Overall, the 90-90-90 goals will be achieved only if HIV testing occurs in safe settings and strategies to ensure linkage to care and retention are put in place.[29]

HIV pathogenesis and immune interventions

Challenges that exist despite access to modern cART include the persistence of inflammation[24] and the existence of HIV reservoirs. Additionally, the absence of an effective immunity against HIV limits the success of HIV vaccine development.

Persistence of immune system abnormalities

Systemic immune activation begins early after infection,[30] characterised by increased proinflammatory mediators, low CD4/CD8 ratios,[31] and exhausted and senescent T cells and monocytes.[32] Chronic inflammation is caused by the direct effects of HIV itself and by chronic co-infections, and predisposes people living with HIV to non-infectious comorbidities, such as cardiovascular diseases and non-AIDS-related cancers.[33] Early cART initiation represents the most effective option to control these deleterious effects.

HIV reservoirs and therapeutic strategies towards HIV cure

One living individual—the Berlin patient[26]—is considered to be cured from HIV, inspiring hope for the patient and research communities 'and the emergence of a global HIV cure research network.[34,35] However, attempts at reproducing a sterilising cure, defined by the complete elimination of replication-competent virus, were unsuccessful.[36] Long-term remission (or functional cure) has been seen in the rare patients known as post-treatment controllers, who, despite the absence of protective HLAs and of robust HIV-specific CD8 cells, can control HIV replication for several years after interrupting cART that was initiated during acute infection.[37,38] Similar long-term remission occurred in early treated children for up to 12 years after cART discontinuation and the Mississippi baby was free of viraemia for 3 years after stopping cART.[39–41]

The absence of standardised methods to quantify the HIV reservoir is an issue in research to find a cure for HIV. Available methods typically assay the total or integrated HIV DNA in infected cells or the replication-competent HIV reservoir detected in resting cells,[42–44] but these methods are imperfect, since the HIV reservoir is mainly in the lymphoid tissues.[45] Most of our knowledge so far comes from studies of blood reservoirs, which show a rapid and massive spreading of clonal viruses during the first 2 weeks after infection.[46,47] The reservoirs decay much more rapidly if cART is introduced early[48] than during chronic infection,[49] from as many as one in ten infected memory T cells, to one infected memory T cell per million CD4 T cells.[46,50] Besides their main localisation in resting central memory CD4 cells,[46,50,51] HIV reservoirs are particularly concentrated in some small subsets, such as the memory stem cells[52] and the follicular T-helper cells.[53–55] The reservoirs are particularly enriched in CD4 T cells displaying several immune check points (eg, PD-1, CTLA-4, TIGIT)[56,57] or CD32a.[58]

Two major mechanisms allow the indefinite persistence of HIV reservoirs, despite apparently optimal ART, as summarised in figure 2.[34,35,59] First, HIV latency—defined as HIV DNA integration into the host genome without virus production—is ensured by complex mechanisms that silence viral transcription[59,60] in resting cells,[60,61] or by immune mechanisms, such as cellular immune checkpoint, which switch off exhausted activated lymphocytes.[34,62] Second, there is additional evidence suggesting that low level virus replication persists in tissues, thus reseeding HIV reservoirs.[63,64]

Reducing the HIV reservoirs alone might not be sufficient to eradicate HIV, as shown by the rapid viral rebound following interruption of cART in chronically

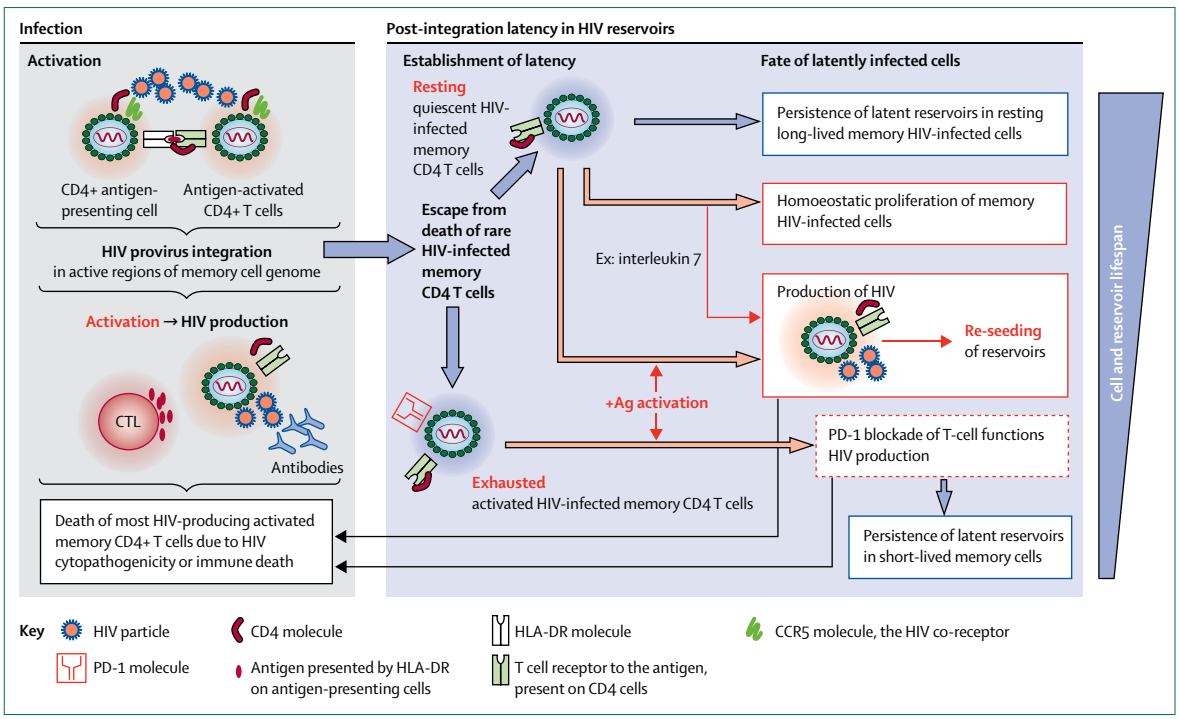

Figure 2: **Main mechanisms of HIV persistence in latent reservoirs**
Schematic representation of: active infection of CD4+ immune cells followed by HIV provirus integration, mainly in the genome of memory T cells, then by HIV production when cells are activated, leading to the death of most HIV-producing cells and the escape of rare HIV-infected cells; post-integration latency in HIV reservoirs; establishment of latency in memory CD4 T cells that are either resting or exhausted and negatively regulated by immune checkpoints; fate of reservoirs in latently infected cells in resting cells in which the long-term resting status allows long-term stable reservoirs, or the homoeostatic proliferation allows proliferation of reservoirs with scarce HIV production, or the antigen-activation induces cell death and reseeding of new HIV reservoirs; and in exhausted cells where immune checkpoints block HIV production, thus inducing persistence of HIV reservoirs. The main therapeutic targets towards HIV cure include: antiretroviral therapy, reversion of latency in resting cells mainly by epigenetic modifiers, immune check points inhibitors restoring HIV production capacity, and anti-HIV immunity mediated either by cytotoxic T cells or antibodies induced by therapeutic vaccines or passive transfers of antibodies.

infected individuals with almost undetectable peripheral blood HIV DNA.[65] Synergistic approaches, such as the so-called shock and kill concept, aim to purge HIV reservoirs by combining the reactivation of latent HIV in infected cells with the killing of HIV-producing cells.[34,35,66] Reactivation of HIV-infected cells was first explored with several latency-reversing agents, such as vorinostat, panobinostat, disulfiram, or romidepsin, or with interleukin 7; all failed to significantly decrease HIV reservoirs.[67–70] Similarly, reinforcing anti-HIV cellular immunity with therapeutic vaccines alone also failed to substantially affect levels of HIV reservoirs.[71–73] Encouraging preliminary data on cellular immunity[73–75] and HIV reservoirs[77] have emerged from studies of the use of immune checkpoint inhibitors in people living with HIV treated for cancer.

Developing vaccines against HIV

An ideal vaccine against HIV remains elusive. Nevertheless, a new paradigm appeared after the relatively successful Thai RV144 trial showed that the amount of non-neutralising antibodies to HIV was a better correlate of protection against infection than T cells.[78] Consequently, extensive characterisation of broadly neutralising antibodies (bNabs) resulted in an exhaustive mapping of key neutralising epitopes on the HIV envelopes that guided the design of novel modified envelopes that were able to induce targeted bNabs in animal models.[78–82] Clinical trials are now evaluating the use of therapeutic monoclonal bNabs with potent antiviral effects, particularly those tested in combinations.[83–85] Novel recombinant viral vector vaccines using a recombinant canarypox or the adenovirus-modified vaccinia virus Ankara plus adjuvant envelopes[86,87] are also currently under investigation in two large preventive vaccine efficacy trials in sub-Saharan Africa (NCT02968849 and NCT03060629). Potential new vaccines are also being tested in combination with shock and kill approaches, with encouraging results in animal models,[35,88,89] and are under evaluation in humans (NCT03041012).

Prevention strategies

Mother-to-child transmission

One of the earliest and greatest successes in the field of HIV prevention has been the prevention of mother-to-child transmission. This success is attributable to the impressive scale-up of cART in priority countries, where 88% of pregnant women with HIV live. In 2016, 76% of

pregnant women with HIV had access to cART, and mother-to-child transmission rates globally fell below 5%, although a few countries continued to lag behind.[13] In high-income settings, mother-to-child transmission rates are now close to zero for women on successful cART before pregnancy.[90] To eliminate mother-to-child transmission, more than 95% of pregnant and breastfeeding women with HIV need to be diagnosed, provided with cART, and to have access to plasma HIV RNA monitoring.[91] Strategies to close the remaining gaps should include (but not be restricted to) implementation of routine and repeated HIV screening in antenatal and postnatal care settings, along with services to enhance retention in care.

Sexual transmission

In addition to condoms and male circumcision,[92] pre-exposure prophylaxis (PrEP) is an additional tool for the prevention of HIV transmission. PrEP is intended to prevent HIV infection in individuals at high risk of acquiring the virus (figure 3). Encouraging results from simian models were followed by several studies confirming the efficacy of tenofovir disoproxil fumarate plus emtricitabine in preventing HIV infection in MSM, heterosexual serodiscordant couples, and heterosexual individuals with multiple partners, when given on a continuous daily basis.[93–96] Poor efficacy of oral tenofovir disoproxil fumarate plus emtricitabine was shown in a large study of women, mainly because of poor adherence.[97] Indeed, adherence is key in achieving high levels of protection with PrEP. The predicted efficacy of daily tenofovir disoproxil fumarate plus emtricitabine in the iPREX study[98] increased from 44% to over 90% when adherence (based on intracellular concentration of the active form of tenofovir) was accounted for. To improve adherence to PrEP, a sex-driven (ie, choosing to use PrEP before and after high-risk sexual encounters only), on-demand, intermittent approach has been tested and yielded 86% protection in MSM at a high risk of acquiring HIV;[99] however, intermittent sex-driven PrEP is not widely used because of scarce data and insufficient evidence about other high-risk populations. Adherence issues are also being addressed through investigational long-acting antiretroviral drugs[100] or subcutaneous implants. The most developed of these drugs is intramuscular long-acting cabotegravir administered every 8 weeks, which is being compared in two large trials to once-daily tenofovir disoproxil fumarate plus emtricitabine in high-risk HIV seronegative men and women (HPTN 083, NCT02720094 and HPTN 084, NCT03164564).

In real-life settings, PrEP has been taken up widely in some MSM communities and resulted in a decrease in the number of new HIV diagnoses.[101–103] A 40% decrease in new diagnoses has been reported for two consecutive years in London, UK,[101] and new HIV infections are declining steadily in San Francisco, USA,[103] although not as rapidly among the city's African-American population as it is among other ethnicities. Broader PrEP scale-up has become imperative to further control the HIV epidemic and needs political commitment, such as that of Paris, France, and other cities engaging in the Fast-Track Cities initiative (ANRS-Prevenir programme in Paris, NCT03113123). Education of high-risk groups through social media and other networks, together with the availability of generic formulations of tenofovir disoproxil fumarate plus emtricitabine, should help expand the reach of PrEP. As the use of PrEP expands, particular attention will need to be given to other sexually transmitted infections.[104]

For more on **Fast-Track Cities** see http://www.fast-trackcities.org/

Other PrEP modalities under investigation include topical medications, such as vaginal or rectal gels and devices, of which the most developed is the dapivirine vaginal ring.[105] Strategies controlled by women, such as vaginal rings or gels, are particularly needed in settings where partner violence, underage sex, early marriage, and other forms of female disempowerment are major contributors to the HIV epidemic. However, unlike oral PrEP in women,[106] the effectiveness of topical PrEP with vaginal gel might be hampered by vaginal microbiota as described with tenofovir-based vaginal gel.[107] HIV prevention strategies should be coupled with other interventions that are essential for positive behavioural changes, such as addressing attitudes and skills (eg, towards safe sex and condom use), decision-making skills and empowerment (eg, knowing a woman's sexual rights), gender norms and roles, communication skills (eg, disclosure), implementation of a personalised risk reduction plan, social support, and having a positive view of women's sexuality.[108]

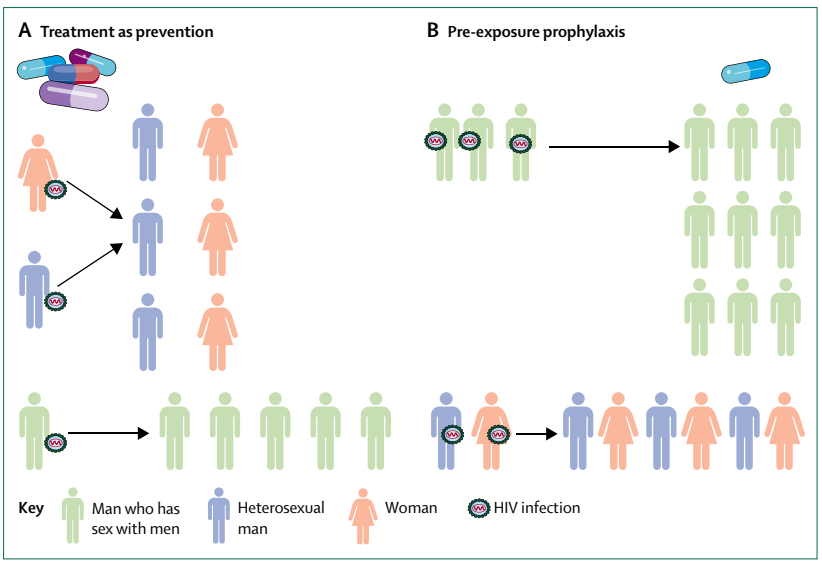

Figure 3: **Treatment as prevention and pre-exposure prophylaxis**
(A) Treatment as prevention involves treating HIV seropositive individuals with suppressive antiretroviral therapy to protect their HIV seronegative sexual partners from acquiring HIV infection. (B) Pre-exposure antiretroviral-based prophylaxis is given to HIV seronegative individuals to prevent viral acquisition from HIV seropositive sexual partners.

Antiretroviral therapy

In the absence of a cure, the goal of HIV treatment is to maximally suppress viral replication and maintain plasma HIV-1 below the level of detection with cART. Further, since cART does not eliminate non-replicating provirus, lifelong cART is mandatory to ensure viral suppression. The overall success of a cART regimen can be viewed in terms of its ability to suppress viral replication without resistance, minus associated costs, which include toxicity, long-term adverse effects, drug interaction risk, and impact on quality of life.

Standard three-drug cART options are improving

In the past two decades, all antiretroviral therapy guidelines have recommended initiating cART with three active drugs, comprising two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) plus a third drug, which has either been a boosted protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI), and, in the past decade, an integrase inhibitor. Commonly used NRTI combinations have changed from thymidine analogues to nucleoside or nucleotide analogues, with less mitochondrial toxicity such as abacavir or tenofovir, a potent drug with activity against HIV and hepatitis B virus that is useful in settings with a high prevalence of co-infection with both viruses, such as sub-Saharan Africa and Asia. Tenofovir disoproxil fumarate, the first available and still widely used tenofovir prodrug, is expected to be replaced in most settings by tenofovir alafenamide, which has better renal and bone toxicity profiles.[109] There have been changes in boosted protease inhibitor use as well with lopinavir plus ritonavir remaining commonly used in resource-limited settings, while other countries have largely moved to darunavir plus ritonavir, which has the highest genetic resistance barrier among boosted protease inhibitors, or atazanavir plus ritonavir, which has some metabolic advantages over other boosted protease inhibitors. Cobicistat, a comparable pharmacoenhancer to ritonavir, has benefits because it is more amenable to co-formulation than ritonavir. The biggest advantage of boosted protease inhibitors is their unique barrier to resistance. Because of their high potency and tolerability by patients, integrase inhibitors have grown in popularity, including for women.[110,111] Elvitegravir plus cobicistat, like raltegravir, produces excellent viral suppression and is highly tolerable,[112,113] and raltegravir is now available in a once-daily formulation.[114] Dolutegravir, with a better resistance profile than raltegravir and elvitegravir, has shown superiority to efavirenz-based and darunavir plus ritonavir-based regimens, partly because it has better tolerability.[115,116] Bictegravir is very similar to dolutegravir, both structurally and in virological efficacy,[117–119] in addition to having an at least comparable in-vitro resistance profile.[120] Co-formulated bictegravir, alafenamide, and emtricitabine offers a new treatment option for a broad range of people living with HIV.

The most recent guidelines for first-line therapy differ between countries. While the US guidelines have opted for an integrase inhibitor-based strategy, European or French guidelines allow tenofovir disoproxil fumarate or tenofovir alafenamide plus either rilpivirine (an NNRTI) or boosted darunavir (a boosted protease inhibitor) or one of the integrase inhibitors.[11] WHO still recommend an NNRTI-based strategy of tenofovir disoproxil fumarate plus emtricitabine (or lamivudine) plus efavirenz; dolutegravir or low-dose efavirenz are alternatives.[12] If current trends continue, the integrase inhibitor class could become the dominant choice globally in coming years.

Single-tablet regimens with three drugs, through brand or generic formulations, are highly recommended as first-line therapy to optimise adherence, a key determinant of treatment success and prevention of resistance. Accumulation of resistance during virological failure in plasma and cellular archives is a major threat to suppressive therapy, as it narrows treatment options and increases treatment costs, particularly in developing countries.[121] Currently, all strategies (ie, NNRTI-based, protease inhibitor-based, or integrase inhibitor-based regimens) are available in single-tablet formulations.

The success rate of first-line cART—where success is defined as a plasma viral load below 50 copies per mL at week 48—has improved in the past 5 years from 70–80% with earlier regimens, to nearly 90% or above.[109,115–119,123,123] Improved immunological and virological profiling of patients initiating cART in the past decade has also benefited treatment outcomes. Overall, the new drugs have pushed the field close to the ceiling of efficacy with respect to viral suppression and allowed improvements in safety and other costs, but additional progress might be within reach.

Investigational HIV treatment strategies

Considerable research attention is now focused on determining how HIV therapy can be improved upon and better individualised (eg, according to age, co-morbidities, and concomitant medications), while reducing lifetime exposure to antiretroviral drugs and associated costs.

Initiation therapy

The GARDEL study was the first large clinical trial to show the non-inferiority of a dual regimen (lopinavir and ritonavir plus lamivudine) compared with a three-drug standard of care.[124] Subsequently, in a 2017 study, boosted darunavir plus lamivudine led to viral suppression in 95% of cART-naive patients after 24 weeks of therapy, comparable to triple therapy.[125] Dual therapies with unboosted integrase inhibitors, however, offer potential tolerability-related and metabolic advantages, as well as fewer drug–drug interactions. Two pilot studies have shown the potential benefits of initial dolutegravir plus lamivudine.[126] Results from two fully powered ongoing

phase 3 randomised trials will be key in assessing whether the paradigm of triple therapy for all, which has prevailed since 1996, can be challenged by dolutegravir plus lamivudine (NCT02831673 and NCT02831764).

Maintenance therapy

There is aggregated evidence to support the notion that once HIV has been well suppressed, viral control can be maintained with reduced antiretroviral burden. Different approaches have been proposed to achieve such reduced burden: antiretroviral dose reduction; a reduction in the number of antiretroviral drugs (eg, through boosted protease inhibitor monotherapy or dual therapy); or a reduction in the frequency of drug administration through intermittent therapy.

Dual regimens containing a boosted protease inhibitor (lopinavir, atazanavir, or darunavir) plus lamivudine have been shown to be non-inferior, and in some cases, superior, to maintenance triple-drug therapy, with efficacy rates above 90–95%. These dual combinations retain the antiviral robustness of regimens that contain boosted protease inhibitors, with no emergence of resistance in the case of viral rebound.[127–129] Interestingly, lamivudine plus a boosted protease inhibitor helped maintain a high level of viral suppression, even in the presence of lamivudine's signature resistance mutation, M184V, in contrast to boosted protease inhibitor monotherapy.[130]

Boosted protease inhibitor-sparing maintenance dual therapies could offer unique benefits. In one study, dolutegravir plus rilpivirine was as effective as triple therapy,[131] and its single-tablet formulation is now approved in the USA. Twice daily raltegravir plus etravirine—an NNRTI with a higher barrier to resistance than rilpivirine—was also highly effective in maintaining viral suppression, with beneficial effects on metabolic parameters and inflammation markers.[132] Similar to initial therapy, preliminary data suggest that dolutegravir plus lamivudine should be effective in maintaining viral suppression;[133] a study with sufficient statistical power is underway.

The development of long-acting drugs given using injections or implants will provide alternative options for patients who report fatigue of routine oral intake. The most advanced long-acting regimen is the dual combination of long-acting cabotegravir—an integrase inhibitor—plus long-acting rilpivirine, now in phase 3 clinical trials, after the successful results of LATTE-2, in which patients received rilpivirine every 4 weeks or every 8 weeks.[134] The feedback from patients suggests that local pain or reactions were largely balanced by the benefit of avoiding daily oral treatment.

Importantly, dual regimens that are free of tenofovir are contraindicated in individuals with hepatitis B virus co-infection, narrowing their potential use in settings with insufficient capacity to prevent or diagnose HBV. There is ongoing research into antiretroviral drugs and delivery modalities that might allow even less frequent dosing, and an array of investigational drugs with established or novel mechanisms of action (table).

Managing HIV in resource-limited settings

Although major strides have been made in improving access to antiretroviral drugs for people living with HIV, insufficient availability and poor affordability of essential medicines, and insufficient access to virological monitoring in many low-income and middle-income countries remain major barriers. Access to second-line and third-line regimens is particularly constrained in resource-limited settings. Accordingly, only 44% (32–53%) of people living with HIV globally were virally suppressed in 2016.[13] Loss to follow-up in the context of a stigmatised lifelong disease is another common reason why people living with HIV might not achieve or maintain viral suppression.[151] The psychosocial and contextual factors that contribute to virological failure are complex, although young age, poor social support, internalised HIV stigma, adverse drug reactions, alcohol consumption, and depression have been documented as predictors of virological failure.[152]

Use of peer support groups, supportive health workers, text message reminders, and reduced waiting times at clinics have proven successful in increasing retention among adolescents and young people living with HIV.[153] To reduce the attrition rates that are particularly high (up to a third of patients) during the period between HIV testing and cART initiation in resource-limited settings, studies have suggested cART initiation on the day of diagnosis.[154] The benefits, feasibility, and ideal population for same day cART initiation need to be further defined and will be dependent on available infrastructure. As ART becomes increasingly widely available, there is a need for a broader adoption of viral load monitoring to maximally reap the benefits of viral suppression and moderate the risk of resistance.[155]

The growing challenges of comorbidities and ageing

People living with HIV are living longer worldwide and half of patients in high-income countries are now aged 50 years or older.[156] Despite this increased survival, the life expectancy of people living with HIV persistently lags behind that of the general population, partly because of their increased risk for comorbidities, which are mediated by traditional risk factors such as smoking, alcohol overconsumption, and illicit drug use, as well as HIV-specific factors, such as the toxic effects of long-term antiretroviral use, persistently heightened inflammation, and immune activation even with effective cART.[157] Non-AIDS co-morbidities of increasing importance include virally mediated cancers (eg, non-Hodgkin lymphoma and anal cancer), other cancers (eg, lung and liver), cardiovascular disease, liver cirrhosis, risk of suicide, and substance use.[157] Hypertension, diabetes, dyslipidaemia, osteoporosis, neurocognitive impairment, chronic renal dysfunction, and frailty are other comorbidities that are

	Description	Phase	Advantages of antiretroviral agent
GS-CA1[135]	Inhibits late-stage virion maturation and post-entry caspid functions	Pre-clinical	First-in-class drug; maintains full activity against HIV-1 mutants resistant to approved antiretrovirals; the pharmacokinetic profile is compatible with long-acting formulation
Combinectin (GSK3732394)[136]	Contains three independent HIV entry inhibitors	Pre-clinical	First-in class recombinant antiretroviral molecule; virus with resistance to any of the three component inhibitors remained susceptible to the recombinant molecule; Combinectin has the potential for use in subcutaneously administered weekly monotherapy
GS-9131[137]	Nucleoside reverse transcriptase inhibitor	Pre-clinical	First reported 10 years ago, this drug's improved resistance profile, compared with currently approved nucleoside reverse transcriptase inhibitors, includes activity against strains bearing common mutations
GS-PI1[138]	Protease inhibitor	Pre-clinical	Has the high resistance barrier of boosted protease inhibitors but does not require boosting
MK-8591 (EFdA)[70,139,140]	Nucleoside reverse transcriptase translocation inhibitor	Phase 1	Potent inhibitor of HIV-1 and the most potent inhibitor of HIV-2 to date; the active triphosphate has extended persistence in mononuclear cells, hence the potential for weekly oral dosing and parenteral dosing every 6 months or less frequently
ABX 464[141]	Inhibits export of unspliced HIV RNA from the nucleus to cytoplasm	Phase 2	First-in-class drug; in addition to reducing viraemia, ABX 464 reduced the viral reservoir in virologically suppressed individuals on ART; the drug has potential applications for a functional cure for HIV
Elsulfavirine[142]	Non-nucleoside reverse-transcriptase inhibitor prodrug of VM 1500A	Phase 2	Comparable virological efficacy to efavirenz but with better tolerability; this drug is being developed for some middle-income countries
Doravirine[142,144]	Non-nucleoside reverse-transcriptase inhibitor	Phase 3	This drug is active against the most common non-nucleoside reverse-transcriptase inhibitor mutations (K103N, Y181C, G190A); it was virologically non-inferior to efavirenz and darunavir plus ritonavir, with a better central nervous system profile than efavirenz and a favourable lipid profile compared with both efavirenz and darunavir plus ritonavir
Bictegravir[117,119,120,145]	Integrase strand transfer inhibitors	Phase 3	Potent unboosted integrase inhibitor with high barrier to resistance; bictegravir was virologically non-inferior to dolutegravir in large trials and showed a similar bone and renal safety profile; the single-tablet formulation of bictegavir, tenofovir alafenamide, and emtricitabine has been submitted for US Food and Drug Administration approval
Cabotegravir[146]	Integrase strand transfer inhibitors	Phase 3	Cabotegravir, an analogue of dolutegravir, is available as either oral or long-acting nanoparticle injection formulations; it has a higher barrier to resistance than raltegravir and elvitegravir, but reduced activity in the presence of some common integrase mutations; it is being developed for prevention and, in combination with long-acting rilpivirine, for maintenance of HIV
Fostemsavir (prodrug of temsavir)[147]	Attachment inhibitor that binds directly to HIV-1 gp120	Phase 3	In a phase 1 study, 15% of participants had decreased viral response to fostemsavir at baseline; fostemsavir showed similar efficacy and tolerability to atazanavir plus ritonavir in ART-experienced individuals, and is being compared to a placebo in a population with multidrug resistance (NCT02362503)
Ibalizumab[148]	Humanised monoclonal antibody to CD4 receptor; blocks post-attachment viral entry	Phase 3	In development for almost 15 years, ibalizumab is active against strains resistant to current antiretroviral drugs; intravenous ibalizumab every 2 weeks plus an optimised background regimen showed promise in a treatment-experienced population
PRO 140[149]	Humanised IgG4 CCR5 monoclonal antibody	Phase 3	In development for over a decade, PRO 140 is being developed as a self-administered weekly subcutaneous injection for CCR5 tropic HIV; it is being investigated in phase 2b/3 studies as maintenance monotherapy (NCT02859961) and in combination with other antiretroviral drugs (NCT02483078)
Albuvirtide[150]	Entry inhibitor	Phase 3	Planned interim analysis of an ongoing study showed weekly intravenous infusion of enfuvirtide plus lopinavir with ritonavir twice daily was non-inferior to lopinavir with ritonavir plus nucleoside reverse transcriptase inhibitors; conditional approval is being sought in China, and a subcutaneous formulation is under development

Table: **Ongoing research into antiretroviral drugs**

more prevalent in people living with HIV than in the general population and contribute directly or indirectly to excess morbidity and mortality.[158,159] The comorbidities in ageing people living with HIV are driven in part by HIV-associated premature ageing.[160] In a large cross-sectional study from Italy, multimorbidity with at least two diseases developed approximately 10 years earlier in people living with HIV compared with HIV-uninfected individuals.[161] Another study found a two-times higher prevalence of diabetes and high prevalence of dyslipidaemia and other cardiovascular risk factors among adults exposed to over 10 years of cART in Malawi, which suggests a widespread effect of comorbidities on HIV outcomes in coming decades.[162] Data from a modelling study predicted that the excess mortality and cardiovascular risk attributable to HIV was similar to that associated with diabetes.[163]

To mitigate the detrimental effect of comorbidities, a global transition to less toxic antiretroviral drugs with lower toxicity and decreased exposure to more toxic antiretroviral drugs is needed urgently, along with adoption of comprehensive interdisciplinary management of comorbidities. Additional focus should be directed towards late presenters and intravenous drug users, since these groups are at a high risk of comorbidities and have not experienced the life expectancy gains seen among people living with HIV generally.[164] Strategies to attenuate the persistent inflammatory state during cART might also help ameliorate the consequences of the increasing age in the population living with HIV.

Conclusion

Although HIV remains a major global concern, substantial progress has occurred in the past 5 years and additional tools are within reach to further control the epidemic. HIV testing should be made available and easy to access everywhere, with subsequent early access to care and cART to optimise survival and prevent transmission. Some of the treatment paradigms under investigation

might be used in clinics worldwide over the next 5 years and enable improved individualised care. Meanwhile, PrEP should be scaled up globally, particularly in high-risk populations, and social factors, such as stigma, that jeopardise success should continue to be dismantled. Collective scientific and social resources will need to be channelled towards achieving the best health and quality of life for ageing people living with HIV. Innovative developments in antiretroviral therapy, including long-acting agents, new delivery modalities, and novel paradigms, such as dual therapy, should be exploited to provide a better quality of life for people living with HIV. Building on knowledge gained over the past two decades, the time has come to intensify multi-pronged, multi-layered approaches, incorporating social ecological interventions (ie, at community, structural policy levels) to achieve broad effects on a population level. Although there is little hope for a sterilising cure or globally effective preventive vaccine in the next decade, a functional cure for HIV might be more realistic to achieve, though daunting obstacles still exist. Having come this far, we should not give up the ultimate goal of ending the HIV epidemic.

Contributors

All authors contributed equally.

Declaration of interests

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