The end of AIDS: HIV infection as a chronic disease

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The success of antiretroviral therapy has led some people to now ask whether the end of AIDS is possible. For patients who are motivated to take therapy and who have access to lifelong treatment, AIDS-related illnesses are no longer the primary threat, but a new set of HIV-associated complications have emerged, resulting in a novel chronic disease that for many will span several decades of life. Treatment does not fully restore immune health; as a result, several inflammation-associated or immunodeficiency complications such as cardiovascular disease and cancer are increasing in importance. Cumulative toxic effects from exposure to antiretroviral drugs for decades can cause clinically-relevant metabolic disturbances and end-organ damage. Concerns are growing that the multimorbidity associated with HIV disease could affect healthy ageing and overwhelm some health-care systems, particularly those in resource-limited regions that have yet to develop a chronic care model fully. In view of the problems inherent in the treatment and care for patients with a chronic disease that might persist for several decades, a global effort to identify a cure is now underway.

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Introduction

The idea of HIV as a chronic disease has emerged as a result of advances in treatment in the past three decades (table 1). Combination antiretroviral therapy (ART) improves health, prolongs life, and substantially reduces the risk of HIV transmission. In both high-income and low-income countries, the life expectancy of patients infected with HIV who have access to ART is now measured in decades, and might approach that of uninfected populations in patients who receive optimum treatment.[1,2]

Advances in treatment and prevention have led some to ask whether the end of AIDS is possible.[3] With the bold assumption that challenges of HIV testing and linkage to care can be overcome, we believe that, although AIDS is now preventable, substantial limitations of present therapeutic approaches persist (figure 1). First, ART does not fully restore health. For reasons that remain to be elucidated, antiretroviral-treated HIV disease is associated with new problems, generally referred to as non-AIDS morbidity. Second, health-care systems in regions where most people with HIV reside (eg, sub-Saharan Africa) were designed to provide acute care only and are ill equipped to provide the chronic care that is now required to manage this disease. Finally, ART is not curative,

meaning that a young adult who acquires HIV will need to take expensive and potentially toxic drugs for several decades—a daunting task for both the individual and the health-care system. In this Review, we argue that although AIDS as a syndrome will diminish in frequency in people identified early and properly treated, solutions to three seemingly disparate issues—HIV-associated inflammation, an overburdened health-care system, and HIV persistence—are needed to further transform HIV disease.

The cascade of care

People have to access and adhere to ART if HIV infection is to become a genuinely chronic disease. Unfortunately, even within the most advanced health-care systems, effective delivery of HIV-related care is far from ideal. The treatment cascade is now a commonly used

Key messages

- HIV-infected individuals with access to modern antiretroviral regimens should be able to suppress viral replication for life, preserve immune function, and avoid most AIDS-related complications
- Antiretroviral therapy does not fully restore health in all individuals; well treated HIV-infected adults have higher than expected risk of several non-AIDS disorders, including cardiovascular disease, kidney disease, liver disease, malignancy, and some neurological diseases
- Although antiretroviral therapy often restores peripheral CD4+ T-cell counts, persistent immune dysfunction, inflammation, and coagulation abnormalities persist and strongly predict risk of non-AIDS morbidity and mortality
- The growing burden of comorbidities in ageing adults will require well resourced health-care delivery systems for chronic care, which are staffed by experts in both infectious and non-infectious complications
- Because antiretroviral therapy must be taken for life, at considerable cost and commitment from the individual, interest is growing in identification of strategies to achieve a functional or sterilising cure
- A few successful reports of functional cure in unique populations (eg, patients with acute infection or bone-marrow transplant recipients) have been reported, but progress to develop a curative intervention that is applicable to most of the infected population has been slow, and a scalable cure is not expected to be available for many years to decades

	Past	Present	Future
Epidemiology	Exponential increase in new infections Disease affects mainly young adults and children Disproportionate burden of new infections in high-risk* populations Life expectancy of less than 2 years after AIDS illness Low proportion of people with access to chronic ART	Fewer new adult infections, but more people living with HIV Disease increasingly common in middle-aged people Reduced number of HIV-infected children; more HIV-exposed uninfected children Disproportionate burden of new infections in high-risk* populations Greater proportion of people treated with ART Life expectancy of decades in treated patients	Few new HIV infections Elimination of HIV infection in children Disease spans age spectrum, with growing burden of disease in geriatric populations More HIV-infected but cured people Few AIDS-related deaths
Immune profile	Severe immune deficiency in untreated patients Partially restored immune deficiency in treated patients	Partially restored immune deficiency with ART Persistent inflammation contributing to incomplete health restoration	Restored immune function through earlier initiation of ART; anti-inflammatory interventions and functional cure in some patients
Disease burden	AIDS-defining illnesses and tuberculosis ART toxicity from early ART combinations	Decreasing AIDS-defining illness with residual persistent tuberculosis risk in ART-treated patients Increasing importance of cardiovascular, liver, renal, and cognitive complications of HIV	Morbidity reflecting age, as seen in HIV-uninfected general population No increased risk for tuberculosis
Health system	Hospital-based detection and care for symptomatic patients	Clinic and hospital based Move towards integrated HIV care cascade	Community-based and clinic-based integrated HIV care model, with specialty HIV cure services

ART=antiretroviral therapy. *Men having sex with men, transgender people, sex workers, injection drug users.
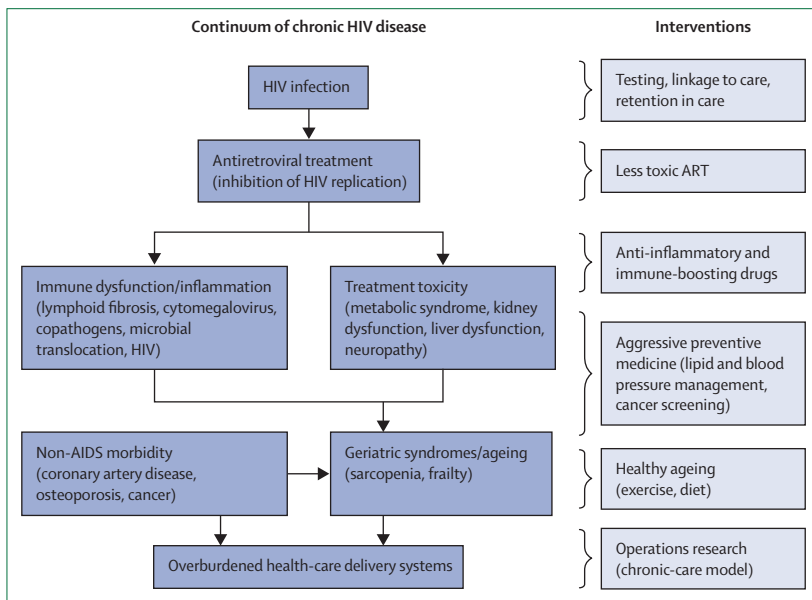
Table 1: HIV as a chronic disease

Figure 1: HIV infection as a chronic disease

Antiretroviral therapy (ART) has transformed HIV infection from a progressive, typically fatal infection to a chronic disease that persists for many decades. A typical young adult who acquires HIV is expected to be on therapy for up to 50 years. Cumulative exposure to antiretroviral drugs or chronic inflammation is expected to have profound effects on health and ageing. Novel health-care delivery systems are needed to provide optimum management of treatment and the many comorbidities associated with HIV disease.

conceptual model that quantifies the delivery of services to people living with HIV across the entire continuum of care.[4] To maximise the benefits of therapy at an individual and community level, at-risk individuals need first to get tested, and those who are infected have to access care, start treatment, stay in care, and remain adherent to HIV therapy. In the USA, for every 100 patients with HIV infection, the US Centers for Disease Control and Prevention (CDC) estimates that only 28 patients have successfully managed each of these steps.[5] The success

rate is much lower in resource-poor regions, particularly sub-Saharan Africa, where identification of HIV status remains a huge challenge.[6]

Disease persists during effective ART

When used correctly, ART results in rapid control of HIV and partial restoration of immune function, leading to prevention of the various complications that define AIDS. However, treatment does not fully restore health. Findings from studies undertaken in high-income countries show that HIV-infected adults who have durable treatment-mediated suppression of HIV replication are at risk for developing several non-AIDS disorders, including cardiovascular disease, cancer, kidney disease, liver disease, osteopenia or osteoporosis, and neurocognitive disease (collectively referred to as serious non-AIDS events). Consider, for example, cardiovascular disease. In a study of the large US-based Veterans Association medical system, HIV-infected adults had about a 1·5-fold increased risk of having a myocardial infarction, after adjustment for traditional risk factors, compared with non-HIV-infected adults.[7] This effect was noted in the subset with durable control of HIV replication, and had an overall effect similar to that for other well accepted risk factors, such as hypertension, hyperlipidaemia, and diabetes. The level of risk attributed to HIV infection was higher in younger people (aged 30–39 years) in this and other studies.[8] Malignancies associated with infections such as human papillomavirus (including urogenital and head and neck cancers), Epstein-Barr virus (including Hodgkin's lymphoma), and hepatitis B and C virus (hepatocellular carcinoma) are also relatively common in HIV-infected adults.

The effect of antiretroviral-treated HIV disease on risk of these non-AIDS events is expected to be similar in high-income and low-income regions, although the nature of this risk in Africa and other low-income

countries has yet to be well defined.[9] One small study that compared cohorts from Botswana to those in the USA showed that crude rates of non-AIDS defining events were similar, but that rates adjusted for age and sex were higher in Botswana.[10] HIV-infected patients are also at risk for diseases such as hypertension and diabetes, both of which are increasingly recognised as major health problems across Africa.[11] Cancer prevention and treatment capabilities in much of Africa are not accessible, irrespective of HIV status. Obesity in those living with HIV is well documented in high-income countries, and is also already a major challenge to African health.[12] Increased smoking in countries such as South Africa is likely to affect the epidemiology of comorbidities seen in chronic HIV infection, including lung, renal, and liver disease, but data are scarce. There is no reason to expect the overall burden of these comorbid disorders to be lower in Africa and elsewhere than in high-income countries. Indeed, in view of the lack of primary prevention, the high burden of inflammatory co-infections, and the fact that therapy is often started late (which is a consistent predictor of developing non-AIDS morbidity[7,13–15]), these age-associated complications are likely to emerge as a major problem as the present generation of relatively young adults begins to age.

Why do antiretroviral-treated adults have an excess risk of these seemingly unrelated non-AIDS events? An excess burden of the traditional risk factors such as smoking, alcohol, and other substance use is almost certainly part of the issue.[16] Direct toxic effects of antiretroviral drugs also contribute to these complications, although each successive generation of ART has been associated with fewer such effects. For example, tenofovir—which is now included in most first-line regimens—and some commonly used protease inhibitors have small but measurable effects on kidney function.[17,18] Metabolic changes, including body fat redistribution (peripheral lipoatrophy and central lipoaccumulation), insulin resistance, diabetes, and hyperlipidaemia are associated with cumulative exposure to ART. Since even small toxic effects might result in large burden of disease when the drugs are used for decades, treatment guidelines now recommend regimens based as much on their long-term toxicity as on antiviral potency.

Traditional risk factors and antiretroviral drug toxicity, however, do not fully explain all the excess risk for non-AIDS morbidity. A rapidly growing and consistent evidence base suggests that many markers of inflammation are higher in antiretroviral-treated adults than in age-matched uninfected individuals.[19,20] Small rises in many of these biomarkers are associated with dramatic increases in the risk of subsequent disease, including all-cause mortality. Of these biomarkers, a series of immune mediators that reflect chronic activation of the innate immune system is key. For example, treated HIV-infected adults have about 50–100% higher concentrations of the inflammatory cytokine interleukin 6 than do well matched
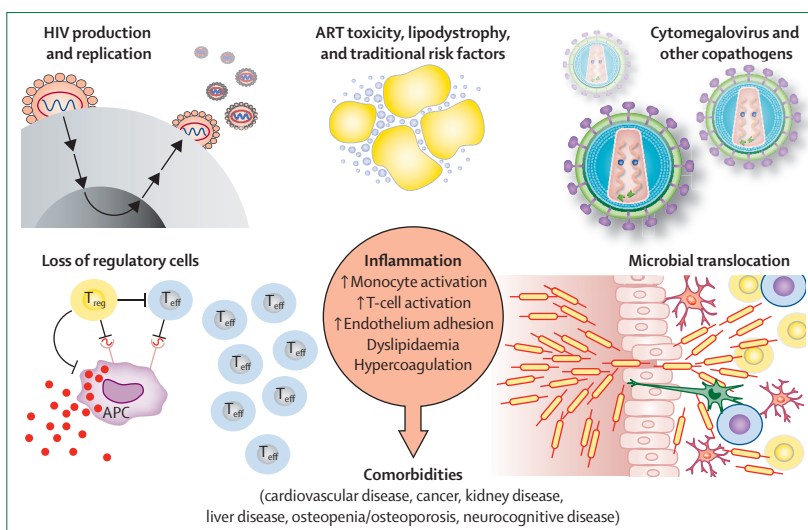

Figure 2: Causes and consequences of HIV-associated inflammation
Despite effective antiretroviral therapy (ART), many if not most HIV-infected adults have evidence of persistent inflammation and immune dysfunction. Root causes of inflammation include ongoing HIV production, high levels of other copathogens, irreversible damage to immunoregulation, and translocation of microbial products across damaged mucosal surfaces. This inflammatory environment causes end-organ damage through several potential pathways. APC=antigen preventing cells. T_{eff}=effector T cells. T_{reg}=regulatory T cells.

uninfected adults.[20] In large international multisite studies (INSIGHT), increases in concentrations of interleukin 6 were strongly associated with all-cause mortality, with odds ratios that were much higher than those recorded in the general population.[21] A single measurement of interleukin 6 predicted excess risk of mortality through several years of observation. Other well validated biomarkers include soluble CD14 and CD163, both of which are released by monocytes or macrophages into plasma upon activation. Increased concentrations of soluble CD14 were associated with increased risk of death in one large study,[22] whereas soluble CD163 has been associated with increased risk of coronary artery inflammation and atherosclerosis.[23] The frequency of inflammatory CD16+ monocytes is also associated with risk of coronary artery progression.[24] Other non-specific markers of inflammation such as C-reactive protein and cystatin C increase more variably during HIV disease.

Measures more directly related to the adaptive immune system also have prognostic importance during treated disease. The rate at which CD4+ T cells increase during ART is highly variable. A few well treated individuals do not achieve normal levels, traditionally defined as greater than 500 cells per µL (although truly normal levels are probably much higher). Risk factors for impaired CD4 T-cell recovery include low pre-treatment CD4+ T-cell count nadir, co-infection with other viruses such as hepatitis C, older age, and perhaps viral factors.[25] Sub-optimum treatment-mediated CD4+ T-cell outcomes probably have clinical consequences in view of the consistent association between CD4+ T-cell counts during ART and increased risk of many comorbidities (eg, heart

disease and cancer) and all-cause mortality.[7,13,14] Chronic signalling through the interferon-α pathway could contribute to this inflammatory disease,[26] as can the effect of virus production or entry (without productive infection) on pyroptosis, which is a highly inflammatory process that can cause death of affected and neighbouring cells.[27] The frequency of activated T cells remains increased during chronic treatment[28] and seems to be related to size of the HIV reservoir and pace of immune reconstitution,[29,30] although the effect of this marker in prediction of overall morbidity and mortality is not as strong as some of the innate immune system inflammatory markers.[31]

Markers of hypercoagulation are also increased in HIV-infected patients receiving ART and are associated with risk of disease progression. D dimers and to a lesser extent fibrinogen concentrations are raised and associated with increased risk of disease.[21,32,33] Lipopolysaccharide, a marker of microbial translocation and at increased concentrations in HIV-infected patients, activates the coagulation process (perhaps via expression of tissue factor activated monocytes[34]), which leads to systemic clotting, tissue damage, and disease.[35] Liver dysfunction leading to altered production of coagulant factors and clearance of lipopolysaccharide can also contribute to this process.[36]

Interest has intensified in definition of the cause and consequence of chronic inflammation during ART (figure 2). Several small biomarker-driven clinical trials have provided insights into why inflammation is increased and how it might be controlled.[37] Intensification of apparently fully effective ART with additional antiretroviral drugs reduces T-cell activation[38] and measures of coagulation,[39] suggesting that low-level HIV replication contributes to the inflammatory process in some patients. Treatment of specific co-infections such as cytomegalovirus[40] and hepatitis C virus[41] reduces T-cell activation, indicating that these common chronic viral infections also contribute to the inflammatory environment during ART. Because HIV-mediated breakdown in the integrity of the gut mucosa and chronic translocation of gut microbial products in the systemic circulation is widely assumed to be a major cause of inflammation,[42] a series of clinical trials reversing this process has been undertaken, with variable success.[43–45] HIV-mediated deposition of collagen in lymphoid tissues is another well established cause of persistent immune dysfunction and inflammation[46] that is actively being addressed in prospective clinical trials.

The use of more broad non-specific immunomodulators aimed at reduction of inflammation is also being investigated. Statins have well established anti-inflammatory effects in the general population, and could have a mortality benefit in HIV disease.[47] Findings from prospective interventional studies have shown promising anti-inflammatory effects.[48] Chloroquine, hydroxychloroquine, COX-2 inhibitors, aspirin, methotrexate, and several other anti-inflammatory drugs are being developed as possible adjuncts to standard antiretroviral drugs (table 2). Interleukin 7 is being developed as means to enhance CD4 T-cell recovery,[49] although interest in this approach is affected by the failure of interleukin 2 to provide clinical benefit in two very large and expensive clinical endpoint studies.[50] There are dozens of promising interventions that might reduce inflammation and inflammation-associated disease burden in development. These phase 1/2-type studies rely almost entirely on biomarkers that have unclear clinical significance. A key question is to decide which if any of these promising drugs should move into clinical endpoint testing, which will be expensive and logistically challenging.

Does HIV infection accelerate ageing?

Because many non-AIDS events are typically associated with ageing in the general population,[51] the popular but vague terms of accelerated ageing or premature ageing are often used to characterise the new range of HIV-associated diseases, but opinions about what defines these terms vary. Whether HIV-associated diseases that have been linked with ageing are simply more common at any given age, or are occurring earlier than expected, is debated. In either case, HIV-infected adults have a high burden of comorbid disorders, including cardiovascular disease, neuropathy, anaemia, osteoporosis, liver disease, and kidney disease. An index designed to characterise the effect of multimorbidity in HIV disease on prognosis has been developed and validated (the VACS index).[52] Multimorbidity, polypharmacy, chronic inflammation, hypercoagulation, and traditional risk factors such as substance misuse are all relatively common in people with HIV, and all are linked to an increased risk of developing the clinical manifestations of ageing in later life in the general population and presumably in the HIV-infected population.[51,53–55]

The controversies and research opportunities provided by the study of ageing and HIV disease are best emphasised by a discussion of frailty. The frailty phenotype is

	Anti-inflammatory drugs	HIV cure interventions
Phase 1	Sevelemer (anti-LPS), anti-PD1 antibody, anti-interleukin-6 antibodies, anti-interferon-α antibodies, sirolimus	Histone deacetylase inhibitors (vorinostat, panobinostat, romidepsin), disulfiram, interleukin 15, anti-PD1 antibody, sirolimus, CCR5-modified T cells and stem cells, therapeutic vaccines, neutralising antibodies
Phase 2	Treatment intensification (ART), statins, aspirin, COX-2 inhibitor, methotrexate, chloroquine/hydroxychloroquine, prebiotics/probiotics, bovine colostrum, rifaximin, aciclovir/valaciclovir, ACE inhibitors/ARBs (antifibrosis), mesalazine (anti-LPS), interleukin 7	Interleukin 7
Phase 3	None	None

LPS=lipopolysaccharide. ART=antiretroviral therapy. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker.

Table 2: Novel therapeutic drugs in development for management of HIV disease

classically defined on the basis of the presence of weight loss, exhaustion, low physical activity, muscle weakness, and slow walking speed.[56] The syndrome is marked by the inability to compensate and maintain normal function (eg, mobility) when confronted with some form of stress (eg, minor surgery, acute infection, or loss of a partner).[53] Frailty emerges when multiple physiological systems begin to decline or fail, leading to a loss of physiological redundancy and an inability to compensate to stress. The greater the number of abnormal physiological systems or diseases such as anaemia, inflammation, cardiovascular disease, or metabolic abnormalities, the more likely one is to be frail.[57,58] Other risk factors for frailty include polypharmacy and social isolation. Since treated HIV disease is now a chronic disorder with many of these risk factors, HIV-infected adults are assumed to have a higher than normal risk for developing frailty as they age.[55] Indeed, despite the relatively young age of most HIV-infected adults, findings from several studies have shown that frailty (or a frailty-like syndrome) is more common in treated HIV disease than in the general population,[59–62] and that, in people with HIV, frailty is associated higher levels of inflammation.[60]

The biology of frailty is the focus of intense research. Many biological factors are known or assumed to contribute to the development of frailty, including chronic inflammation (as measured by interleukin 6 and other biomarkers), hypercoagulability, mitochondrial dysfunction, DNA mutagenesis, alterations in telomerase activity or telomere length phenotype, and endocrinopathies.[63] HIV infection and its treatment detrimentally affects all these pathways.[21,36,64–66] A highly contentious issue for future mechanistic studies is whether there are distinct aspects of HIV disease that fundamentally change the biology of ageing.[65,67]

The health systems gap

HIV disease as a chronic illness requiring lifelong therapy and characterised by multiple comorbidities represents unique problems for health-care delivery. Identification of people with HIV, linking them to care, providing them with access to therapy, and addressing the multiple potential complications requires a well resourced health-care system.[68] Barriers to success exist at every step and have been well documented.[69]

The absence of a well resourced chronic-care model is particularly urgent in resource-limited areas such as sub-Saharan Africa.[70–73] Some of the crucial elements needed for a sustainable HIV chronic-care model in Africa include: efficient, effective, and safe antiretroviral management; services for reproductive health, non-AIDS morbidity such as cardiovascular disease, and ageing; and prevention and treatment services for tuberculosis. The global discourse on health-system strengthening that identified HIV resource allocation as an impediment to progress has been replaced by thoughtful analysis of the architecture of successful systems supported by relatively few resources.[74,75] New models for health-care delivery must build on lessons learned during ART scale-up.[76] Quality improvement programmes will be crucial components of successful chronic care models.[77]

Separation of acute from chronic care is an essential step in the transition to a chronic-disease model. Specialised, largely urban, clinics with staff and a structure meeting the complex medical management of advanced AIDS were important at the launch of antiretroviral programmes. However, as patient populations evolve from those with active AIDS illnesses and low CD4+ T cells requiring physician expertise and long visits to stable, antiretroviral-treated populations, new care models are necessary. These models need to absorb millions more patients into chronic disease care in a sustainable, efficient, and affordable manner. Decentralisation of services, task shifting, and streamlined monitoring have already successfully begun, reducing transport barriers, increasing retention of staff, and reducing costs.[77–80] A shift towards a more community-based model of chronic care will need continued investments in supply-chain management and the development of point-of-care diagnostics. The measurement of HIV RNA concentrations in real time with affordable and sensitive assays that work in several settings—including those without phlebotomy and electricity—is particularly important because such measurements can be used to monitor treatment adherence and establish when therapy needs to be modified.[81]

Despite an ageing population, HIV disease in Africa still predominantly affects young people and adults of reproductive age. Reproductive health services encompassing both ART and family planning are essential components of chronic HIV disease care. Characterisation of drug interactions between treatments required for HIV and those used to prevent pregnancy and other chronic diseases is urgently needed. In an era in which HIV transmission to children can be eliminated with aggressive antiretroviral drug management at birth, future research will need to assess whether exposure to these drugs affects health even as they prevent infection.[82]

Care of an ageing HIV epidemic in Africa has already been raised as an area of concern and unmet need.[83] The increased life expectancy of HIV-infected people receiving ART will result in a progressively older population, with changes in life expectancy already detectable at a population level in South Africa.[84] The number of people older than 50 years living with HIV is expected to triple by 2040 to 9 million, on the basis of estimates of ART coverage that many would consider conservative.[85] Neurocognitive impairment and frailty are more common in elderly people than in younger populations; tuberculosis and other non-communicable diseases will occur with a higher frequency, demanding care systems that address these needs and a research agenda focused on key issues related to an elderly population.

Although many AIDS-related illnesses can be nearly eliminated with successful ART, tuberculosis is an

exception. Tuberculosis rates remain several-fold higher for people with chronic treated HIV infection than for HIV-uninfected people living in the same region.[86] The underlying deficit to explain this vulnerability is unknown, but probably includes factors related to incomplete immune restoration and ongoing inflammation. Isoniazid prophylaxis, tuberculosis screening, and treatment should be incorporated into the chronic-care model through systems that prioritise convenience to the patient.[87]

What are the next steps with regard to HIV as a chronic disease in Africa? That one solution might exist for addressing the present challenge in health delivery for the millions of people with chronic HIV and other non-communicable diseases is a fallacy. The needs of HIV as a chronic disease will be shaped by many factors including background infections (eg, tuberculosis, hepatitis), lifestyles (eg, smoking, obesity), reproductive trends, and socioeconomic structures. The pace of access to the diagnosis and treatment of non-AIDS disease is not predictable and will vary by region. However, a unified approach between the HIV and non-communicable disease communities has a greater chance to accelerate access for both.[88] There is growing scientific work describing the advantages and pitfalls of integrating HIV services with those for other chronic diseases, and a need for rigorous implementation science that measures efficiencies from the perspective of patients, providers, and health systems.[89,90] There needs to be an openness to a variety of models that could work, and consideration of both public-sector and private-sector solutions.[91] That the creation of new systems has emerged as a crucial issue in the next phase of the AIDS response emphasises the success of HIV medicine.

HIV persistence and need for a cure

Despite the clinical effectiveness of ART, disease persists during effective treatment, and delivery of ART on a global level for decades to all in need of therapy will be a daunting and resource-expensive endeavour. Recognition of these limitations has led to growing recognition that a safe, affordable, and effective cure for HIV disease might be needed to address the limitations of present therapeutic strategies.[92] Although a cure for HIV remains an aspirational goal, several clinical findings suggest that it might be possible.

Several mechanisms account for the inability of antiretroviral drugs to eliminate HIV. Despite complete or near complete inhibition of HIV replication with ART, virus persists in long-lived infected resting T cells that contained integrated, transcriptionally silent (or latent) HIV DNA.[93] These memory T cells are designed to persist indefinitely. Other cells that probably harbour HIV during long-term therapy include naive CD4+ T cells and CD4-expressing cells of the monocyte or macrophage lineage.

That a cure is possible was shown by the Berlin patient, who several years ago received an allogeneic haemopoietic stem-cell transplantation for the management of his leukaemia. After extensive conditioning with a myelo-ablative regimen (which probably eliminated much of the HIV reservoir), donor stem cells that were naturally resistant to HIV were successfully transplanted.[94] More than 6 years after the transplantation, he meets any definition of a clinical cure.[95] More recently, two cases of potential cure after myeloablation and allogeneic stem-cell transplantation were identified in Boston,[96] while several groups are attempting to repeat the success of the Berlin patient with similar donors or by gene therapy to make autologous cells resistant to HIV infection. Curing of HIV infection with such interventions is clearly possible, but these intensive, expensive, and potentially life-threatening interventions are unlikely to ever be widely used.

A more promising approach might be to use ART to prevent seeding of the reservoir. The initiation of a potent regimen about 30 h after birth to an infant subsequently shown to be HIV infected seemed to be curative.[97] As a single case, what led to the cure of this infant is unknown, but interest has grown in studies aimed at repeating this finding, and establishing the mechanism for the apparent cure.

Can such an outcome be achieved by aggressive treatment for recently infected adults? A study of adults in Thailand who received therapy within 10–14 days of their exposure showed that HIV DNA could not be detected in the longest lived cells within a few months of start of therapy, raising the possibility that, with time, relatively shorter-lived T cells harbouring the virus might die. In another unrelated study, 14 adults living in France were identified who started therapy during acute or early infection, remained on therapy for several years, stopped therapy for uncontrolled reasons, and did not exhibit any virological rebound, even after a few years of monitoring.[98] Replication-competent virus was detected in these individuals, suggesting that some host mechanism was controlling the virus. Whether early treatment altered their natural history, or whether these 14 individuals would have done well even without treatment, is unknown.

Stem-cell transplantation and very early therapy have shown promise, but none of these studies are relevant for most HIV-infected individuals who started therapy during chronic infection and who do not have any clinical condition that might necessitate a risky stem-cell transplantation. For these individuals, interventions that safely reverse latency while enabling the death of virus-producing cells might be the only viable way to a cure (table 2). Two groups have shown that the chromatin-modifying drug vorinostat—which alters gene regulation and can therefore activate transcription—increases HIV RNA production in resting T cells in long-term treated adults.[99] An increase in detectable virus in plasma was rare, making it unlikely that there were sufficient concentrations of protein made to cause cell death or stimulate a host-immune response. However, in these studies, vorinostat was

given only for a short time. Further studies using a longer duration of vorinostat, more potent activating agents, or combining latency activation with immune stimulation are underway. Other promising approaches to clearing the reservoir are slowly being moved into the clinic (table 2).

Conclusions

By virtue of the success of ART, HIV has evolved into a chronic disease in which the typical complications of AIDS are no longer the dominant problem in many parts of the world. Rather than dealing with acute and potentially life-threatening complications, clinicians are now confronted with managing a chronic disease that in the absence of a cure will persist for many decades. HIV care requires new skills on the part of the clinical workforce and a reshaping of health-care systems that were initially designed for acute care. Clinicians will still require knowledge of antiretroviral management but will need more expertise in prevention and management of cardiovascular disease and other comorbidities, including many of the complications typically associated with ageing. Biomedical research will need to evolve accordingly. Understanding of why inflammation persists during ART, how it causes morbidity, and how to reverse the process is a high priority for HIV disease, as it is for many other chronic disorders. The research community will need to identify optimum, cost-effective ways that integrate services for non-communicable disease and tuberculosis to deliver chronic care to an ageing population who largely reside in areas without solid health-care systems for primary care. Since a cure for HIV infection might prove to be the best solution for all these problems, basic discovery, early clinical investigation, and the establishment of large collaborations that aim to tackle HIV persistence during ART are needed.

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