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The End of AIDS: HIV Infection as a Chronic Disease

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Abstract

Antiretroviral therapy has been a spectacular success. People are now asking if the end of AIDS is possible. For those 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 consequence, a number of inflammation-associated and/or immunodeficiency complications such as cardiovascular disease and cancer are increasing in importance. Cumulative toxicities from exposure to antiretroviral drugs for decades cause clinically-relevant metabolic disturbances and end-organ damage. There are growing concerns that the multi-morbidity associated with HIV disease may impact healthy aging and could overwhelm some health care systems, particularly those in resource-limited regions that have yet to fully develop a chronic care model. Given the problems inherent in treating and caring for a chronic disease that might persist for several decades, a global effort to identify a cure is now underway.

INTRODUCTION

The face of HIV as a chronic disease has changed as a result of advances in HIV treatment in the last three decades (Table 1). Combination ART (ART) improves health, prolongs life and substantially reduces the risk of HIV transmission. In both high and low income countries, the life expectancy of HIV-infected patients who have access to ART is now measured in decades, and may approach that observed in uninfected population among those who are optimally treated(1, 2).

Advances in treatment and prevention have led some to now ask if the “end of AIDS” is possible(3). Making the bold assumption that challenges of HIV testing and linkage to care can be overcome, we are of the opinion that although AIDS is now preventable, substantial limitations of current 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 a new constellation of problems, generally referred to as “non-AIDS morbidity”, and, in the popular press, “premature aging”. Second, health care systems in

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those regions where most people with HIV reside (e.g., sub-Saharan Africa) were designed to provide acute care only and are ill-equipped to provide the chronic care which 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 while AIDS as a syndrome will diminish in frequency among persons identified early and properly treated, solutions to the seemingly three 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 antiretroviral therapy if HIV infection is to become a truly chronic disease. Unfortunately, even within the most sophisticated health care systems, effective delivery of HIV-related care is far from ideal. The “treatment cascade” is now a commonly used conceptual model that quantifies the delivery of services to persons living with HIV across the entire continuum of care(4). In order to maximize the benefits of therapy on an individual and community levels, 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. Currently in the US, for every 100 patients with HIV infection, it is estimated by the Centers for Disease Control (CDC) that only 28 patients have successfully managed each of these steps (REF). The success rate is much lower in resource poor regions of the world, particularly sub-Saharan Africa, where identification of HIV status remains a huge challenge. (5).

DISEASE PERSISTS DURING EFFECTIVE ART

When used correctly, ART results in rapid control of HIV and partial restoration of immune function, leading to the prevention of the various complications that define AIDS. This does not mean that health is fully restored, however. Studies conducted in high income countries tell us that HIV-infected adults experiencing durable treatment-mediated suppression of HIV replication are at risk for developing a number of non-AIDS conditions, including cardiovascular disease, cancer, kidney disease, liver disease, osteopenia/osteoporosis and neurocognitive disease (collectively referred to as “serious non-AIDS events”). Consider, for example, cardiovascular disease. In the large US-based VA medical system, after adjusting for traditional risk factors, HIV-infected adults had about a 1.5 fold increased risk of having a myocardial infarction(6). This effect was seen in the subset with durable control of HIV replication, and had an overall effect comparable to other well-accepted risk factors, such as hypertension, hyperlipidemia and presence of diabetes mellitus. The level of risk attributed to HIV infection was higher in younger persons in this and other studies(7). Malignancies associated with infections such as human papilloma virus (including uro-genital and head and neck cancers), Epstein Barr Virus (including Hodgkins disease), and hepatitis B and C (hepatocellular carcinoma), are also relatively common in HIV-infected adults.

The impact of antiretroviral-treated HIV disease on risk of these non-AIDS events is expected to be similar in high and low income regions, although the nature of this risk in Africa and other low income countries has yet to be well-defined(8). One small study which compared cohorts from Botswana to the US found that crude rates of non-AIDS defining events were similar, but that age and gender adjusted rates were actually higher in Botswana(9). HIV infected patients are not spared the risk for diseases such as hypertension and diabetes, both of which are increasingly recognized as major health problems across Africa(10). Cancer prevention and treatment capabilities in much of Africa are not accessible, regardless of HIV status. Obesity among those living with HIV is well documented in high income countries but is also already is a major challenge to African health(11). Increased smoking in countries such as South Africa is likely to influence the epidemiology of co-morbidities seen in chronic HIV infection including lung, renal and liver disease, but data are lacking. There is no reason to expect the overall burden of these co-morbid conditions to be lower in Africa and elsewhere than in high income countries. Indeed, given 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(6, 12-14)), it must be assumed that these age-associated complications will emerge as a major problem as the current generation of relatively young adults begin 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 abuse is almost certainly part of the issue(15). Direct toxicity of antiretroviral drugs also contributes to these complications, although each successive generation of antiretroviral therapy has been associated with less toxicity. For example, tenofovir—which is now included in most first-line regimens—and some commonly used protease inhibitors have subtle but measurable effects on kidney function(16, 17). Metabolic changes, incuding body fat redistribution (peripheral lipoatrophy, central lipoaccumulation), insulin resistance, diabetes mellitus, and hyperlipidemia are associated with cumulative exposure to antiretroviral therapy. Since even subtle toxicities 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 their antiviral potency.

Traditional risk factors and antiretroviral drug toxicity, however, do not fully explain all of the excess risk for non-AIDS morbidity. A rapidly growing and remarkably consistent evidence base indicates that many markers of inflammation are higher in antiretroviral-treated adults than in age-matched uninfected individuals(18, 19). Subtle elevations in many of these biomarkers are associated with dramatic increases in the risk of subsequent disease, including all-cause mortality. Key among these biomarkers is a series of immune mediators that reflect chronic activation of the innate immune system. For example, as compared to a well-matched uninfected population, treated HIV-infected adults have approximately 50 to 100% higher levels of the inflammatory cytokine interleukin-6 (IL-6)(19). In large international multi-site studies (INSIGHT), elevations in IL-6 levels were strongly associated with all-cause mortality, with odds ratios that were much higher than that observed in the general population(20). A single determination of IL-6 predicted excess risk of mortality through several years of observation. Other well-validated biomarkers include

soluble CD14 (sCD14) and sCD163, both of which are released by monocytes/macrophages into plasma upon activation. Elevated levels of sCD14 was associated with increased risk of death in one large study(21) while sCD163 has been associated with increased risk of coronary artery inflammation and atherosclerosis(22). The frequency of “inflammatory” CD16+ monocytes is also associated with risk of coronary artery progression(23). Other non-specific markers of inflammation such as C-reactive protein and cystatin C are more variably increased during HIV disease.

Measures more directly related to the adaptive immune system also have prognostic significance during treated disease. The rate at which CD4+ T-cells increase during ART is highly variable. A minority of well-treated individuals fail to achieve normal levels, traditionally defined as anything above 500 cells/ul (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(24). Suboptimal treatment-mediated CD4+ T cell outcomes likely have clinical consequences given the consistent association between CD4+ T cell counts during ART and elevated risk of many co-morbidities (e.g., heart disease, cancer) and all-cause mortality(6, 12, 13). Chronic signalling through the interferon-alpha pathway may contribute to this inflammatory disease(25), as can the impact of virus production/entry (without productive infection) on pyroptosis, which is a highly inflammatory process that can cause death of affected and neighbouring cells(26). The frequency of activated T cells remains elevated during chronic treatment(27) and appears related to size of the HIV reservoir and pace of immune reconstitution(28, 29), although the effect of this marker in predicting overall morbidity and mortality is not as strong as some of the innate immune system inflammatory markers (30).

Markers of hypercoagulation are also elevated in HIV-infected patients on ART and associated with risk of disease progression. D-dimers and to a lesser extent fibrinogen levels are elevated and associated with increased risk of disease(20, 31, 32). It has been postulated that lipopolysaccharide (LPS), a marker of microbial translocation and increased in HIV-infected patients, activates the coagulation process (perhaps via expression of tissue factor activated monocytes)(33) and that this leads to systemic clotting, tissue damage and disease(34). Liver dysfunction leading to altered production of coagulant factors and clearance of LPS may also contribute to this process(35).

There is intense interest in defining the cause and consequence of chronic inflammation during ART (Figure 2). A number of small biomarker-driven clinical trials have provided insights into why inflammation is elevated and how it might be controlled(36). Intensification of apparently fully effective ART with additional antiretroviral drugs reduces T-cell activation(37) and measures of coagulation(38), suggesting that low-level HIV replication contributes to the inflammatory process in some patients. Treating specific co-infections such as CMV(39) and hepatitis C virus(40) reduces T-cell activation, indicating that these common chronic viral infections also contribute to inflammatory environment during ART. As 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(41), a series of clinical trials reversing this process have been

performed, with variable success(42-44). HIV-mediated deposition of collagen in lymphoid tissues is also another well-established cause of persistent immune dysfunction and inflammation(45) that is actively being addressed in prospective clinical trials.

There is also intense interest in the use of more broad non-specific immunomodulators aimed at reducing inflammation. The statins have well-established anti-inflammatory effects in the general population, and may have a mortality benefit in HIV disease(46). Promising anti-inflammatory effects have been observed in prospective interventional studies(47). Choloroquine, hydroxychloroquine, COX-2 inhibitors, aspirin, methotrexate and a number of 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(48), although interest in this approach is affected by the failure of interleukin-2 to provide clinical benefit in two very large and expensive clinical end-point studies(49). There are dozens of promising interventions which might reduce inflammation and inflammation-associated disease burden in development. These phase I/II-type studies rely almost entirely on biomarkers that have unclear clinical significance. A key question for the field is to decide which if any of these promising drugs to move into clinical endpoint testing, which will be an expensive and logistically challenging study to complete.

DOES HIV INFECTION ACCELERATE AGING?

Because many of these non-AIDS events are typically associated with aging in the general population(50), the popular but vague terms “accelerated aging” or “premature aging” is often used to characterize the new spectrum of HIV-associated diseases, but there are mixed opinions on what defines these terms. There is ongoing debate as to whether HIV-associated diseases which have been associated with aging are simply more common at any given age, or are occurring earlier than expected. In either case, it is well accepted that HIV-infected adults have high burden of co-morbid conditions, including cardiovascular disease, neuropathy, anemia, osteoporosis, liver disease and kidney disease. An index designed to characterize the impact of multi-morbidity in HIV disease on prognosis has been developed and validated (the VACS Index)(51). Multi-morbidity, polypharmacy, chronic inflammation, hypercoagulation, and traditional risk factors such as substance abuse are all relatively common in the HIV infected population, and all are linked to greater risk of developing the clinical manifestations of aging in later life in the general population and presumably in the HIV-infected population (50, 52-54).

The controversies and research opportunities provided by the study of aging and HIV disease is best illustrated by a discussion of frailty. The frailty phenotype is classically defined based on the presence of weight loss, exhaustion, low physical activity, muscle weakness and slow walking speed (55). The syndrome is marked by the inability to compensate and maintain normal function (e.g., mobility) when confronted with some form of stress (e.g., minor surgery, acute infection or loss of a partner)(52). Frailty emerges when multiple physiologic systems begin to decline or fail, leading to a loss of physiologic redundancy and an inability to compensate to stress. The greater the number of abnormal physiologic systems or diseases such as anemia, inflammation, cardiovascular disease, or metabolic abnormalities, the more likely one is to be frail(56, 57). Other risk factors for

frailty include polypharmacy and social isolation. Since treated HIV disease is now a chronic condition with many of these risk factors, it is reasonable to assume that HIV-infected adults have higher than normal risk for developing frailty as they age(54). Indeed, despite the relatively young age of most HIV-infected adults, a number of studies have found that frailty (or a frailty-like syndrome) is more common in treated HIV disease than in the general population(58-61), and that among those with HIV, frailty is associated higher levels of inflammation(59).

The biology of fraily is the focus of intense research. Many biologic factors are known or assumed to contribute to the development of frailty, including chronic inflammation (as measured by IL-6 and other biomarkers), hypercoagulability, mitochondria dysfunction, DNA mutagenesis, alterations in telomerase activity/telomere length phenotype and endocrinopathies(62). HIV infection and its treatment impacts in a potential detrimental manner all of these pathways(20, 35, 63-65). A highly contentious issue ripe for future mechanistic studies is whether there are distinct aspects of HIV disease that alters the biology of aging in some fundamental manner (64, 66).

THE HEALTH SYSTEMS GAP

HIV disease as a chronic illness requiring life-long therapy and characterized by multiple co-morbidities represents unique problems for health care delivery. Identifying 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(67). Barriers to success exist at each step and have been well documented(68).

The lack of a well-resourced chronic care model is particularly urgent in resource-limited areas such as sub-Saharan Africa (69-72). Some of the critical elements needed for a sustainable HIV chronic care model in Africa include (1) efficient, effective and safe antiretroviral management, (2) services for reproductive health, non-AIDS morbidity such as cardiovascular disease, and aging and (3) fail safe TB prevention and treatment services. The recent global discourse on “health systems strengthening” that singled out HIV resource allocation as an impediment to progress has been eclipsed by thoughtful analysis of the architecture of successful systems supported by relatively few resources(73, 74). New models for health care delivery must build upon lessons learned during antiretroviral scale up while incorporating new concepts such as quality improvement “dashboards” for clinical care. Separating acute from chronic care is an essential step in the transition to a chronic disease model. Specialized largely urban clinics with staff and a structure catering to the complex medical management of advanced AIDS made sense at the launch of antiretroviral programs. As patient populations evolve from those with active AIDS illnesses and low CD4+ T cells requiring physician expertise and long visits to one enriched with stable, antiretroviral treated patient 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. Decentralization of services, task shifting and streamlined monitoring has already successfully begun, reducing transport barriers, increasing retention and reducing costs(75-77). Shifting towards a more community-based model of chronic care will require continued investments in supply chain management and the development of point-

of-care diagnostics. The measurement of HIV RNA levels in real time using affordable and sensitive assays that work in a variety of settings—including those without phlebotomy and electricity—is particularly important as such measurements can be used to monitor treatment adherence and determine when therapy needs to be modified(78).

Despite an aging population, HIV disease in Africa still predominantly affects youth and adults of reproductive age. Reproductive health services encompassing both ART and family planning are essential components of chronic HIV disease care. Characterization of drug interactions between treatments required for HIV and those used to prevent pregnancy and other chronic diseases are urgently needed. In an era where HIV transmission to children can be eliminated with aggressive antiretroviral drug management at birth, future research will need to address whether exposure to these drugs impact health even as they prevent infection(79).

Care of an aging HIV epidemic in Africa has already been raised as an area of concern and unmet need(80). The increased life expectancy of HIV infected persons receiving ART will result in a progressively older population, with changes in life expectancy already detectable at a population level in South Africa(81). The number of persons over 50 years of age living with HIV is expected to triple by 2040 to 9 million persons, based on estimates of ART coverage that many would consider conservative(82). Neurocognitive impairment and frailty is more common in the elderly; 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 this population.

Although many AIDS related illnesses can be nearly eliminated with successful ART, tuberculosis is an exception. Tuberculosis rates remain several-fold higher for persons with chronic treated HIV infection compared to HIV uninfected persons living in the same region(83). The underlying deficit to explain this vulnerability is unknown but likely includes factors related to incomplete immune restoration and ongoing inflammation. On a practical level, isoniazid prophylaxis, TB screening, and treatment should be incorporated into the chronic care model through systems that prioritize convenience to the patient(84).

What are the next steps with regard to HIV as a chronic disease in Africa? A single solution to the current challenge in health delivery for the millions with chronic HIV and other non-communicable diseases is a fallacy. The needs and face of HIV as a chronic disease will be shaped by many factors including background infections (e.g. tuberculosis, hepatitis); lifestyles (e.g., 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(85).There is a growing literature describing the advantages and pitfalls of integrating HIV with other chronic care and a need for rigorous implementation science that measures efficiencies from perspective of the patients, providers and health systems(86, 87). There needs to be an openness to a variety of models that could work and consideration of public as well as private sector solutions(88). It is indeed a reflection of success in HIV medicine that the

creation of new systems has emerged as a critical issue in the next chapter of the AIDS response.

HIV PERSISTENCE AND NEED FOR A CURE

It is hard to overstate the clinical effectiveness of ART. Still, as outlined above, disease persists during effective ART and delivering 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 may be needed to address the limitions of current therapeutic strategies (89). Although a cure for HIV remains an aspirational goal, a number of recent observations in the clinic suggest 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(90). These memory T-cells are designed to persist indefinitely. Other cells that likely harbour HIV during long-term therapy include naïve CD4+ T cells and CD4-expressing cells of the monocyte/macrophage lineage.

That a cure is possible was demonstrated by the "Berlin Patient", who several years ago received an allogeneic hematopoietic stem cell transplant for the management of his leukaemia. After extensive conditioning with a myeloablative regimen (which likely eliminated much of the HIV reservoir), donor stem cells that were naturally resistant to HIV were successfully transplanted(91). He is now more than six years out from the transplant and meets any definition of a clinical cure(92). More recently, two cases of potential cure after myeloablation and allogenic stem cell transplant were identified in Boston(93), while several groups are attempting to repeat the Berlin Patient experiment using similar donors or by gene therapy to make autologous cells resistant to HIV infection. Curing HIV infection with such interventions is clearly possible, but these intensive, expensive and potentially life-threatening interventions are unlikely to be ever widely used.

A more promising approach may be to use ART to prevent seeding of the reservoir. The initiation of a potent regimen approximately 30 hours after birth to an infant subsequently shown to be HIV infected appeared to be curative (REF). As a single case, it is unknown what led to a cure of this infant, but there is intense interest in studies aimed repeating this observation, and determining the mechanism for the apparent cure.

Can such an outcome be achieved by aggressively treating recently infected adults? Provocative data in this regard were provided in a study of adults in Thailand who received therapy within 10 to 14 days of their exposure. Within a few months of starting therapy, HIV DNA could not be detected in longest lived cells, raising the possibility that with time, the relatively shorter-lived T-cells harbouring the virus might die off, recapitulating the cured baby story. In another unrelated study, 14 adults living in France were identified who (1) started therapy during acute/early infection, (2) remained on therapy for several years, (3) stopped therapy for a variety of uncontrolled reasons, and (4) failed to exhibit any virologic rebound, even after a few years of observations(94). Replication-competent virus

was detected in these individuals, suggesting that some host mechanism was controlling the virus. It remains to be determined as to whether early treatment altered their natural history, or whether these 14 individuals were destined to be “elite” controllers and would have done well even without treatment.

Stem cell transplants and very early therapy have shown promise, but none of these studies are relevant to the vast majority of HIV infected individuals who started therapy during chronic infection and who lack any clinical condition that might necessitate a risky stem cell transplant. For these individuals, interventions that safely reverse latency while enabling the death of the virus-producing cells might be the only viable way to a cure (Table 2). Two groups have recently 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(95). An increase in detectable virus in plasma was rare, making it unlikely that there were sufficient levels of protein made to cause cell death or stimulate a host immune response. However, in these studies, vorinostat was only given for a short period of time. Further studies using 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 (see Table 3).

CONCLUSIONS

By virtue of the success of ART, HIV has evolved into a chronic disease in which the typical complications AIDS are no longer the dominant problem in many parts of the world. Rather than dealing with acute potentially life-threatening complications, clinicians now are 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 those health care systems initially designed for acute care. The clinician of the future will still require knowledge of antiretroviral management but will need more expertise in preventing and managing cardiovascular disease and other co-morbidities, including many of the complications typically associated with aging. Biomedical research will need to evolve accordingly. Understanding 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 conditions. The research community will also need to identify optimal, cost-effective ways that integrate non-communicable disease and TB services to deliver chronic care to an aging population who largely reside in areas that lack solid primary care health care systems. Since curing HIV infection might prove to the best solution for all of these problems, basic discovery, early clinical investigation, and the establishment of large collaborations aimed at tackling HIV persistence during ART are needed.

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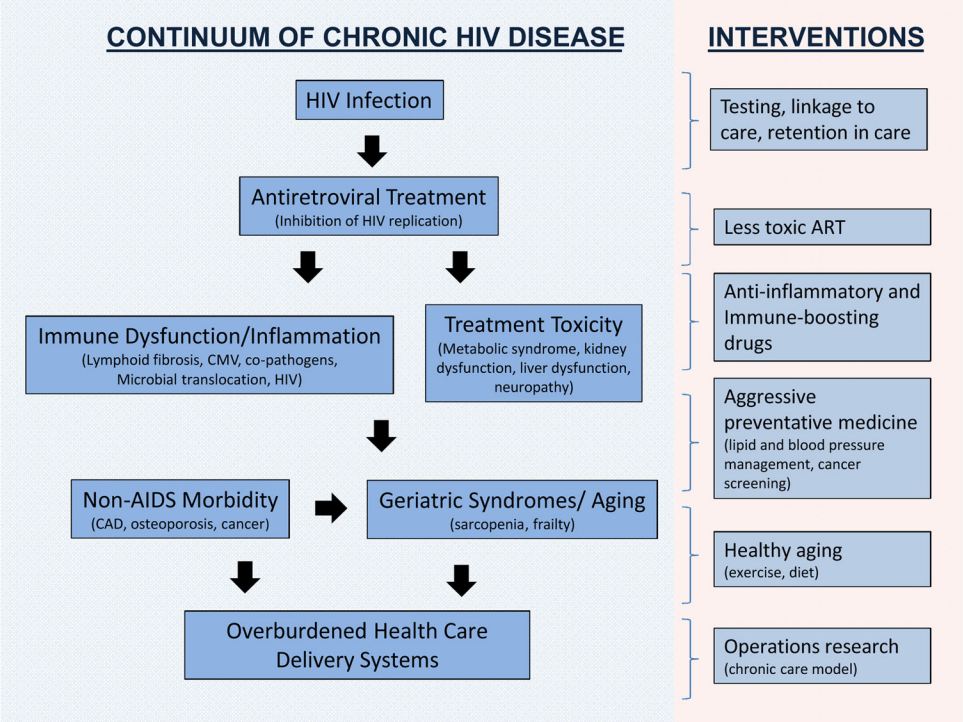

Figure 1. HIV Infection as a Chronic Disease

Antiretroviral therapy 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 and/or chronic inflammation is expected to have profound effects on health and aging. Novel health care delivery systems are needed to provide optimal management of treatment and the many co-morbidities associated with HIV disease.

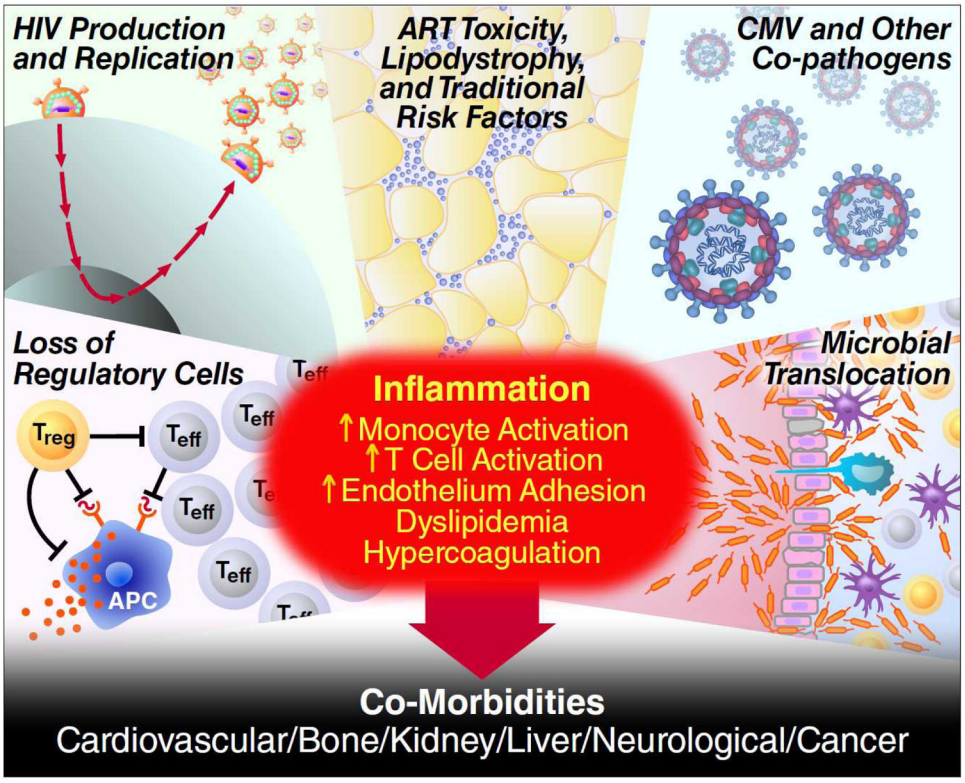

Figure 2. Causes and consequences of chronic inflammation during antiretroviral treatment

Causes and Consequences of HIV-associated Inflammation. Despite effective antiretroviral therapy, 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 co-pathogens, irreversible damage to immunoregulatory system, and translocation of microbial products across damaged mucosal surfaces. This inflammatory environment causes end-organ damage through several potential pathways.

Table 1

HIV as a Chronic Disease

	Past	Present	Future
Epidemiology	• Exponential increase in new infections • Disease affects primarily young adults and children • Disproportionate burden of new infections among high risk* populations • Life expectancy of less than 2 years after AIDS illness • Low proportion of persons with access to chronic ART	• Fewer new adult infections, but more living with HIV • Disease increasingly observed in middle age • Reduced number of HIV infected children; more HIV-exposed uninfected children • Greater proportion of persons treated with ART • Life expectancy of decades among treated persons	• Few new HIV infections • Elimination of HIV infection among children • Disease spans age spectrum, with growing burden of disease in geriatric populations • More HIV infected but cured persons • Few AIDS related deaths
Immune Profile	• Severe immune deficiency among untreated patients • Partially restored immune deficiency among 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 • Antiretroviral therapy toxicity from early ART combinations	• Decreasing AIDS defining illness with residual persistent TB risk in ART treated • 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 and clinic based integrated HIV care model with specialty HIV cure services

* Men having sex with men (MSM), transgender, sex workers, injection drug users

Table 2

Novel therapeutic drugs in development for management of HIV disease

	Anti-inflammatory Drugs	**HIV Cure Interventions**
Phase I	• Sevelemer (anti-LPS) • Anti-PD-1 antibody • Anti-IL-6 antibodies • Anti-interferon-alpha antibodies • Sirolimus	• HDAC inhibitors (vorinostat, panobinostat, rhomedepsin) • Disulfiram • Interleukin-15 • Anti-PD-1 antibody • Sirolimus • CCR5-modified T cells and stem cells • Therapeutic vaccines • Neutralizing antibodies
Phase II	• Treatment intensification (ART) • Statins • Aspirin • COX-2 inhibitor • Methotrexate • Choroquine/hydroxycloroquine • Prebiotics, probiotics • Bovine colostrum • Rifaximin • Acyclovir/valacyclovir • ACE inhibitors/ARBs (anti-fibrosis) • Mesalamine (anti-LPS) • Interleukin-7	• Interleukin-7
Phase III	• None	• None