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HIV and Ageing: Emerging Research Issues

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Abstract

Purpose of the review—It is now widely accepted that HIV-infected individuals remain at higher risk for mortality and age-related morbidities than the general population, but several unresolved issues need to be addressed by the research community in the coming years to further improve the health of HIV-infected individuals in the modern treatment era.

Recent findings—While recent studies have helped better define the contribution of HIV to life expectancy and morbidity in the modern ART era, questions remain about the generalizability of these findings to a future HIV-infected population that is expected to be much older. Furthermore, while a consensus has emerged that the persistent inflammatory state contributes to morbidity and mortality in this setting, the relative contributions of this process, health-related behaviors, co-morbidities, and medication toxicities remain incompletely understood. Lastly, significant uncertainty remains over the root causes of the persistent inflammatory state, the specific immunologic pathways to target with interventions, and the most appropriate biomarkers to use for surrogate outcomes in pilot trials of immune-based interventions.

Summary—Each of these issues will be addressed in this review, highlighting recently published and presented studies that inform the discussion, and recommendations will be made for prioritizing the future research agenda.

Keywords

HIV-1; inflammation; aging; multi-morbidity; mortality; antiretroviral therapy

Introduction

HIV-infected individuals have experienced a dramatic improvement in life expectancy in the modern antiretroviral therapy (ART) era, particularly those who initiated therapy at early disease stages [1, 2]. Nevertheless, millions of HIV-infected individuals around the world – and millions more to come – will have initiated ART at advanced disease stages and appear to be at substantially higher risk of morbidity and mortality than the general population, even when sustained viral suppression is achieved [3]. There is now an emerging consensus that the persistent inflammatory state contributes to this increased risk [4]. This inflammation-associated risk of morbidity and mortality is also superimposed on an aging HIV epidemic in both resource-rich and resource-limited settings as individuals live longer

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on ART, potentially amplifying the risk of age-related morbidity. Much progress has been made in understanding the probable causes of excess morbidity and mortality in treated HIV infection, but several unresolved issues remain to be addressed to further improve the health of HIV-infected individuals receiving ART.

The scope of the problem

A broad consensus now exists that HIV-infected individuals in the modern treatment era have a higher risk of mortality and age-associated multi-morbidity than the general population [5–9]. This excess HIV-associated risk of morbidity and mortality will almost certainly become a greater public health issue as more HIV-infected individuals enter their sixth and seventh decades of life. Indeed, half of all HIV-infected individuals in the United States are expected to be over the age of 50 within the next few years [10], as will many more millions of HIV-infected individuals in resource-limited settings around the world [11, 12]. Nevertheless, significant uncertainty remains over whether inferences from recent cohort studies will accurately reflect a future HIV-infected population that is expected to be much older.

For example, several recent cohort studies have suggested that the life expectancy of HIV-infected individuals may approach that of the general population, particularly among those who initiated ART at earlier disease stages [1, 13–15]. These projections assume that the risk of mortality in the relatively small proportion of older individuals in contemporary cohort studies will reflect the risk actually observed in the future population. This may not be a safe assumption. As antiretroviral treatment regimens have become more effective and less toxic, and more patients initiate ART at earlier disease stages, it is possible that the risk of morbidity and mortality might be lower for older HIV-infected individuals in the future. On the other hand, most of the current older population of HIV-infected individuals survived the pre-ART and early ART eras and may well be enriched for favorable host genetics and healthier lifestyles than the general population. Such a survivorship bias might result in a significant underestimation of the influence of HIV on morbidity and mortality in older populations. Indeed, given the approximately 50% increased risk of coronary artery disease in the HIV-infected population after adjustment for traditional cardiovascular risk factors [16, 17], as well as a potentially even greater relative risk of sudden cardiac death [18], it seems likely that recent life expectancy projections for the HIV-infected population may well be overly optimistic. This may be particularly true if the impact of HIV on multi-morbidity and life expectancy increases with age, though most clinical cohorts currently have too few HIV-infected individuals in their sixth and seventh decades to definitively assess whether this might be the case. It will also take time before the leading edge of older HIV-infected patients in most cohorts is no longer strongly influenced by survivorship bias issues.

Does HIV Cause Accelerated Aging or Increased Co-Morbidity?

While it is well established that HIV-infected individuals have a higher risk of several age-related co-morbidities than the general population, there has been considerable debate as to whether HIV causes accelerated aging [7]. This is in part because “aging” itself is difficult

to define, but also because the framing of the debate depends on one's perspective. For example, if one wants to improve the overall health and quality of life of a frail HIV-infected individual with multiple co-morbidities, then the recognition that this clinical phenotype is similar to that observed in much older geriatric populations is helpful. Minimizing pill burden, overlapping toxicities, and drug interactions; avoiding destructive health-related behaviors; and focusing on interventions like moderate exercise that holistically address overall function rather than specific disease states are all valuable lessons from the geriatrics literature that are likely to be helpful for frail HIV-infected individuals. On the other hand, if the goal is to identify targets for interventions to prevent multi-morbidity and frailty in HIV infection, then understanding the specific diseases that are increased as well as the mechanisms that drive them is critical. Here, specificity is important. For example, while many non-AIDS cancers are in fact increased in HIV-infected individuals with a history of AIDS, not all age-related cancers are increased, and some cancers (i.e., breast, prostate, and colon) may even be decreased [19]. While surveillance bias may have led to under-reporting of some cancers in patients with AIDS, it is notable that a similar pattern of cancer incidence – both those that are increased and decreased - is observed in other inflammatory diseases like rheumatoid arthritis [20]. Here, recognizing the differences between the effects of HIV and aging on cancer incidence may actually provide clues as to the pathophysiology and highlight targets for interventions. Similarly, our group recently demonstrated that the phenotypic CD8+ T cell defects observed in treated HIV infection are actually quite distinct from those observed in aging and have qualitatively different effects on mortality risk [21, 22]. Thus, while the clinical features of multi-morbidity in HIV and aging may be similar, their root causes may be different and understanding those differences may help identify more appropriate interventional targets to prevent multi-morbidity from developing in the first place. A better understanding of the shared and distinct determinants of multi-morbidity and frailty in HIV and aging is thus clearly needed to identify the most appropriate interventional targets.

Relative importance of inflammation as a target for interventions

While there is now a broad consensus that immune activation and inflammation persist in the majority of HIV-infected individuals maintaining long-term ART-mediated viral suppression – even in those that restore normal CD4+ T cell counts [23–26], and that immune activation and inflammatory markers strongly predict morbidity and mortality and even frailty in this setting [27–37], the degree to which inflammation is a direct cause of morbidity and mortality in this setting remains controversial. A prominent role of the inflammatory state in explaining the excess morbidity and mortality observed in treated HIV infection is supported by several observations. First, the relationship between inflammatory markers and mortality is much stronger in treated HIV infection than it is in the general population [32, 38], consistent with a more central role of the inflammatory state in driving mortality risk in this setting. Second, while confounding medication toxicities may play a role, it is notable that other inflammatory diseases like rheumatoid arthritis and psoriasis are associated with similar magnitude increases in cardiovascular disease, osteoporosis, and lymphoma [20, 39–43], consistent with a role of systemic inflammation in promoting chronic disease. Indeed, each of the surrogate markers of end-organ disease (i.e.,

hemoglobin, creatinine, and transaminase levels) that contribute to the prognostic utility of the Veterans Aging Cohort Study (VACS) index is strongly associated with markers of inflammation, monocyte activation, and coagulation [31], underscoring the link between the inflammatory state and dysfunction of multiple organ systems in HIV infection.

Nevertheless, it remains unclear how much of the increased morbidity and mortality in treated HIV infection is attributable to the inflammatory state as opposed to confounding lifestyle factors, co-morbidities, or antiretroviral medication toxicities. Often, studies comparing HIV-infected and –uninfected individuals lack sufficient granularity in confounding risk factor assessment and/or are too small to completely exclude confounding by these factors. That said, some potential confounding co-morbidities like diabetes and hypertension may also be in part a consequence of the HIV-induced inflammatory state [44, 45], so adjustment for these factors may underestimate the true effect of HIV-associated inflammation on clinical events [46]. Furthermore, the effects of lifestyle factors on clinical outcomes might even be modified by HIV infection. For example, one recent study suggested that the relationship between smoking and atherosclerosis is stronger in HIV-infected than HIV–uninfected individuals [47]. Smoking may also cause monocyte activation, inflammation, and hypercoagulability, so it is perhaps not surprising that HIV may amplify its effects on cardiovascular risk [48]. HIV also tended to increase the impact of hypertension on myocardial infarction risk in the VACS, though this interaction did not reach statistical significance [49]. Similarly, moderate exercise has long been known to decrease inflammation and improve both cognitive function and overall health in elderly populations, and has recently been shown to decrease inflammation in a pilot trial of much younger HIV-infected individuals [50]. Thus, lifestyle changes may have an even more important impact on health in HIV-infected individuals than in the general population, in part because they decrease the inflammatory state.

Definitive evidence that inflammation causes excess morbidity and mortality in treated HIV infection will only come from a large clinical trial of a specific immune-based intervention that reduces clinical events in this setting. Unfortunately, few candidate interventions to date are both scalable and have promising enough immunologic effects in pilot studies to warrant investing in expensive clinical endpoint trials. A clinical endpoint trial of statins is being considered in treated HIV infection based on observational studies suggesting benefit [51–53], and clinical trials demonstrating favorable immunologic effects in HIV infection [54, 55]. Nevertheless, even if statins are shown to decrease cardiovascular events in HIV-infected individuals who don’t otherwise meet criteria for statin therapy, questions might remain about the extent to which reductions in clinical events are due to a declines in inflammation or cholesterol, as they have following statin trials in the general population [56]. The inferences might be more compelling if non-cardiovascular endpoints are also decreased by statins (e.g., cancer, bone fractures, etc). Indeed, rosuvastatin improved bone mineral density in a recent clinical trial of ART-suppressed individuals, though it was not clear whether this was mediated by immunologic mechanisms [57]. Other commonly used medications with anti-inflammatory properties (e.g., aspirin, angiotensin converting enzyme inhibitors, etc) have also shown some promise in HIV-infected individuals in small pilot studies [58, 59], but given cost constraints and research capacity issues, the threshold for advancing these interventions to clinical endpoint trials is likely to be high.

Earlier initiation of ART in the course of HIV infection is also likely to reduce the inflammatory set-point during ART-mediated viral suppression [22, 60, 61], and a clinical trial of early vs. later ART initiation (the Strategic Timing of AntiRetroviral Treatment, START, NCT00867048) is underway. This trial might also help inform whether reducing inflammation (via earlier ART initiation) decreases the risk of non-AIDS events. Nevertheless, inflammation continues to predict morbidity and mortality for at least a decade during treated HIV infection [62], so it is possible that the effects of chronic inflammation on morbidity and mortality may not be evident until trial subjects reach older ages, years after the trial ends. Indeed, the rate of non-AIDS events in the enrolled population is apparently lower than originally anticipated when START was planned [63].

Identifying the most appropriate targets for interventions

While the above interventional strategies currently being pursued are promising, it is unlikely that any of them are likely to completely reverse the persistent inflammatory state of treated HIV infection. Thus, developing more effective interventional strategies is a major focus of the field. Identifying the most appropriate specific targets for interventions to pursue - even in small pilot trials - remains a challenge, however, particularly in an era of constrained resources. Studies linking biomarkers to clinical events have therefore taken on increasing importance to identify those pathways that are most likely to drive disease. Two recent studies determined that soluble markers of innate immune activation predicted non-AIDS events and mortality during ART-mediated viral suppression much more strongly than T cell activation and senescence [64, 65]. These studies suggest that innate immune activation may be a more relevant target for interventions than T cell activation or senescence, but there remains a myriad of potential innate immunologic pathways that could be targeted [27–37].

To better prioritize potential interventional targets, it may be helpful to consider not just the individual relationships between specific biomarkers and clinical outcomes, but also how they fit together in biologic systems in vivo. Just because a particular inflammatory marker is strongly associated with clinical outcomes, it may not necessarily be the most appropriate direct target for interventions. For example, the inflammation reflected by IL-6 levels and coagulation reflected by D-dimer levels may be along the final common pathway linking immune activation to disease, but specifically blocking IL-6 signaling or coagulation might not reverse morbidity and mortality if the underlying causes of the inflammatory state are not addressed as parallel inflammatory pathways may persist or even increase (the “whack-a-mole” theory). Mediation and pathway modeling approaches may well prove useful in drawing inferences from these studies about the most promising interventional targets. Indeed, targeting the root causes of the inflammatory state may prove to be a more sensible strategy, even if the biomarkers that reflect those root causes tend to be less strongly associated with clinical outcomes.

Several root causes of the persistent inflammatory state during suppressive ART have been proposed including HIV itself (either from residual low-level replication [66–69] or passive release from infected cells), co-infections like cytomegalovirus (CMV) or hepatitis C virus (HCV) [70, 71], and microbial translocation [72]. Unfortunately, except for anti-HCV

therapy, we currently lack safe and effective interventions to potently block these root causes. While ART intensification may decrease the extent of low-level HIV replication in a subset of patients (particularly those for whom penetration of antiretroviral medications into lymphoid tissues may be incomplete [66–69]), its impact on systemic immune activation is modest at best, and no currently available medications block HIV release from infected cells. While drug development for CMV is quite active, we currently lack safe therapies that can be given to ART-suppressed individuals long-term. Furthermore, microbial translocation has proven to be difficult to reverse in HIV-infected individuals [73–76], perhaps since HIV-associated microbial translocation involves defects at multiple levels (e.g., gut epithelial barrier integrity and function, immune surveillance in lamina propria, lymphoid tissues, etc) [77]. To overcome this challenge, one might need to combine synergistic interventions that address each one of these defects simultaneously. Alternatively, simply treating individuals with anti-inflammatory interventions for much longer durations of time may be required to reverse microbial translocation. Indeed, chronic immune activation and inflammation may not only impair immune function, but they may also directly cause gut epithelial barrier defects [78–80]. Just as it appears to take at least six months for systemic microbial translocation to fully ramp up during primary HIV infection [81], it may take several months of reducing inflammation before gut barrier integrity is noticeably restored. Thus, further research is required to develop more effective interventions to reverse the underlying causes of the inflammatory state in treated HIV infection.

Choosing the most appropriate surrogate markers in clinical trials

Just as there remains uncertainty as to the most appropriate interventional targets, the most appropriate surrogate markers to use in pilot trials of immune-based interventions also remains uncertain. The lack of a single stable, reproducible, and reliable surrogate marker for the persistent inflammatory state in treated HIV infection also limits the possibility for novel drug development in this area. Many of the biomarkers that most strongly predict mortality in treated HIV infection (e.g., IL-6, D-dimer, etc.) fluctuate greatly within individuals and typically require excessively large sample sizes for adequate power to detect clinically relevant effects in pilot trials. Conversely, T cell activation, which is much more stable within individuals and has been effectively used as a surrogate outcome in many prior pilot trials, fails to reliably predict clinical outcomes in treated HIV infection [64, 65]. Considering biomarkers in the context of in vivo systems may also be helpful here as some soluble markers of monocyte activation (e.g., sCD14, sCD163) reflect a key source of inflammation and coagulation in HIV infection [82], and predict mortality [83], but are also relatively stable within individuals and can be measured reliably in small pilot trials [84]. Thus, these biomarkers will likely be used more commonly in future pilot trials of immune-based interventions. An alternative approach would be to create an index of several biomarkers predictive of mortality in this setting, as has recently been proposed by the INSIGHT network [62], though more information is needed on the within-subject variability over time for such indices for these approaches to be effectively compared.

Conclusion

As the HIV epidemic ages, the impact of HIV on multi-morbidity and premature mortality is likely to take on increasing public health importance. Understanding the similarities between the multi-morbidity associated with HIV and aging may help frame the clinical management of frail HIV-infected patients, while understanding the differences in the root causes of multi-morbidity in HIV and aging may help better focus our attention on targets for interventions to prevent future morbidity and mortality in HIV-infected individuals. The persistent inflammatory state of treated HIV infection is likely to be an important determinant of morbidity and mortality, and it may even interact with health related behaviors, such that smoking cessation, diet, and exercise may be even more important interventions for HIV-infected patients than the general population. Better understanding the root causes of the persistent inflammatory state in treated HIV infection and developing more effective interventions for these targets will continue to be an important research agenda for the next several years.

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Key Points

- HIV is associated with an increased risk of multi-morbidity and mortality, which is likely to take on increasing public health importance as the HIV epidemic gets older.
- While the clinical phenotype of HIV-associated multi-morbidity shares many features with aging-related frailty, its root causes may in fact be distinct, requiring different interventions for prevention.
- Persistent inflammation is likely to be a major driver of morbidity and mortality in treated HIV infection, and a better understanding of its root causes may help prioritize targets for interventions.
- Recent studies have also helped shape our understanding of the most appropriate surrogate biomarkers to employ in pilot studies of immune-based interventions.