HIV Elite Controllers – the Issue at Heart

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ABSTRACT

Background: People with HIV are living longer, and as this population age, chronic diseases associated with aging, such as cardiovascular disease, will become of great importance. HIV controllers (ECs) are a small subset of the HIV population, who maintain viral suppression without anti-retroviral therapy. Despite non-medical viral control and the absence of physician-related opportunistic infections, their protective immune activation places them at greater risk for coronary atherosclerosis, compared to their non-progressing viral counterparts (1).

Objective: To summarize data from a systematic review to collect evidence pointing to an association between elite controller status and increased risk of coronary atherosclerosis.

Methods: A structured literature review was conducted using three databases: Scopus, PubMed, and Web of Science. The findings were restricted to journal articles published between 2000-2016. Keywords used for the searches were “elite” AND “controller” AND “coronary” OR “atherosclerosis”. A total of 4 articles were selected based on the keywords. Article references were screened to include two more articles. The references from these were screened for a total of 6 articles meeting inclusion and exclusion criteria.

Results: Upon review of the articles, both the support that ECs have a higher risk of coronary atherosclerosis then medically controlled HIV viremtic patients, one shows no association. Three articles were inconclusive, two because of mixing of results for ECs with viremtic controllers (another subpopulation of HIV patients) and one requiring following up reviews.

Conclusion: The findings suggest that there may be an association between HIV EC status and cardiovascular risk, compared to coronary atherosclerosis mediated by immune activation to chronic viral infection.

INTRODUCTION

WHO ARE ELITE CONTROLLERS? (ECs)

Elite Controllers (ECs) are a rare and unique subset of the HIV population representing less than 1% of all HIV-infected individuals. This group of HIV “nonprogressors” is defined by their ability to maintain an undetectable viral load using clinical assays (HIV RNA <50 copies/mL) without the use of antiretroviral therapy (7). The mechanism for this viral control is still unknown (6). This spontaneous control of HIV has been subject to investigation for a potential “functional cure” of HIV; control of viral replication without the use of antiretroviral therapy (8).

WHY IS CORONARY ATHEROSCLEROSIS A CONCERN IN THIS POPULATION? (ECs)

Despite their apparent ability to control the HIV virus, studies have found evidence to suggest ECs exhibit ongoing inflammation due to chronic immune activation and low viral replication. This may carry a higher risk for inflammation-associated vascular dysfunctions when compared to HIV-infected individuals (9).

OBJECTIVE:

This structured literature review will investigate the association between ECs and coronary atherosclerosis, one of the most prevalent forms of heart disease and a leading cause of death. These findings may be used to evaluate standards of care and may suggest treatment to improve the prognosis of ECs.

RESEARCH QUESTION:

Do HIV elite controllers have a higher risk of coronary atherosclerosis than medically controlled HIV viremtic patients?

METHODS

A search of three databases, was conducted from the dates of September 28th 2016 to November 9th 2016. The databases included Scopus, PubMed, and Web of Science. The structured literature review was conducted in the same manner for each database, selecting inclusion and exclusion criteria. Terms were searched for in the title, abstract, and keywords, and included “elite” AND “controller” AND “coronary” OR “atherosclerosis”. Using SCOPUS as an example; these terms resulted in six matches. Exclusion criteria were applied to the results in four acceptable articles. References were reviewed and two more articles were found that met the inclusion criteria. References were reviewed for these articles to exclude non-qualifying articles. The reference search did not produce any new leads. Six articles were analyzed by two investigators. Each investigator had the same items of focus, and comparisons were later conducted to determine the final conclusion.

Inclusion criteria:

• Elite AND controller AND coronary OR cardia
• elite controller AND coronary OR cardia must be present in body of article
• Term: atherosclerosis is also acceptable
• Other controller terminology accepted as long as controller terminology was defined

• Publications: 2000-2015
• English language only

Exclusion criteria:

• Viremic controller
• Long-term nonprogressor
• Other chronic inflammatory diseases
• Assessment of non-HIV patient population only
• Article not peer reviewed
• Did not compare EC to medically controlled HIV population

RESULTS

Table: Study Type, Population, Purpose, Preliminary Findings, Conclusions, Limitations, Association

<table>
<thead>
<tr>
<th>Study</th>
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<th>Population</th>
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<th>Preliminary Findings</th>
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<tbody>
<tr>
<td>Crowell et al. (2016)</td>
<td>Prospective Cohort</td>
<td>38 HIV controllers (viremic): 69% male, mean age 46yo, mean viral load &lt;50 copies/mL, median time post infection</td>
<td>To characterize the rates and reasons for hospitalization among HIV Controllers and patients with medically controlled HIV in a cohort from U. S. military personnel and veteran Affairs Clinical Centers</td>
<td>Fewer hospitalizations among elite controllers compared to viremic controllers.</td>
<td>No significant difference in hospitalization rates between HIV+ Controllers and HIV+ Viremic patients.</td>
<td>The study was not adequately powered to detect differences in hospitalization rates between HIV+ and viremic patients.</td>
<td>INCONCLUSIVE</td>
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<td>Crowell et al. (2015)</td>
<td>Retrospective Cohort</td>
<td>183 HIV+ Controllers: 64% male, mean age 45yo, mean viral load 45,000 copies/mL</td>
<td>To use a multivariate, incident cohort of HIV+ patients to compare hospitalization rates among ECs with those of HIV+ patients with medically controlled and uncontrolled HIV+</td>
<td>ECs had the highest all-cause hospitalization rates of all groups, with the highest hospitalization rates in those with viremic controllers.</td>
<td>Cardiovascular disease was the most common reason for hospitalization, accounting for 30% of admissions.</td>
<td>Potential for selection bias cage data being limited to persons actively engaging in HIV care.</td>
<td>YES</td>
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<td>Krahn et al. (2014)</td>
<td>Experimential</td>
<td>66 HIV Controllers: 67% male, mean age 45yo, mean viral load 45,000 copies/mL</td>
<td>To observe if there is a significant increase in inflammatory biomarkers in ECs compared to HIV- and non-HIV controls.</td>
<td>ECs had a significant increase in inflammatory biomarkers compared to HIV- and non-HIV controls.</td>
<td>ECs had higher rates of hospitalization due to coronary heart disease.</td>
<td>Requires further study to consider clinical implications.</td>
<td>INCONCLUSIVE</td>
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<td>Vollenweider et al. (2013)</td>
<td>Case-Control Study</td>
<td>574 HIV Controllers: 54% male, mean age 45yo, mean viral load 45,000 copies/mL</td>
<td>To determine the incidence of non-AIDS events was similar in ECs, viremic controllers, and noncontrollers.</td>
<td>Incidence rate of non-AIDS events was similar in ECs, viremic controllers, and noncontrollers.</td>
<td>No significant increase in the incidence of non-AIDS events in ECs compared to HIV- negative controls.</td>
<td>Small sample size.</td>
<td>INCONCLUSIVE</td>
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<td>Perny et al. (2011)</td>
<td>Cross-Sectional</td>
<td>64 ECs: 60yo, 59% male, mean viral load &lt;50</td>
<td>To determine the contribution of immune activation to the increased atherosclerosis of HIV-infected patients.</td>
<td>No difference in plaques between HIV-1 chronic, and non-AIDS conditions.</td>
<td>Did not control for smoking factors, alcohol, hypertension.</td>
<td>Small sample size.</td>
<td>YES</td>
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<tr>
<td>House et al. (2009)</td>
<td>Cross-Sectional</td>
<td>31 HIV+ (VL&lt;50): median age 45yo, 70% M, 42% viremic</td>
<td>To compare the contribution of immunity and biomarkers of HIV- associated atherosclerosis.</td>
<td>Carotid intima-media thickness (IMT) and C-Reactive protein (CRP) were higher in ECs compared to HIV-negative controls.</td>
<td>Carotid IMT was higher in all HIV+ groups, regardless of CRP levels.</td>
<td>INCONCLUSIVE</td>
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DISCUSSION

2 of 6 studies linked HIV EC status with an increased risk of coronary atherosclerosis, compared to HIV+ viremic patients; one showed no increase in risk; while 3 were inconclusive.

Lack of data on smoking. Lack of data on smoking.

The two affirmative studies were observing a different rate (risk, incidence, or prevalence), and the positive results give greater weight to our hypothesis, however, the inconclusive and contradictory results indicated further testing is required to confirm these findings.

The difficulty of enrolling ECs into studies due to their independence from ART was indicated by Crowell (2015), and could be the primary reason many studies have difficulty confirming a causal link between HIV EC status and atherosclerosis.

There was conflicting information about the hospitalization rates among ECs. The study with no association did indicate an increased risk of atherosclerosis in HIV EC patients compared to non-medically controlled HIV viremic patients, however the risk was negligible compared to medically controlled HIV patients. There was overlap in the three studies measuring hospitalization that ECs have a greater amount of coronary atherosclerosis than HIV-positive counterparts.

There are few in the HIV community and may be underrepresented due to not seeking care, unlike their HIV viremtic counterparts.

CONCLUSION

There may be an association between ECs and an increase in risk of coronary atherosclerosis compared to individuals with medically controlled HIV.

It is evident that ECs are at a greater risk for coronary atherosclerosis than seronegative individuals.

ECs may benefit from cardiovascular management interventions.

EC may also benefit from ART.

Further research is needed on this topic to better assess the health implications of ECs.