

# Considerations for the clinical management of elite controllers

## Questions

- What is the prevalence of elite controllers among people living with HIV?
- What are the specific considerations regarding diagnostic testing of elite controllers?
- What is the recommended clinical management of elite controllers?

## Key Take-Home Messages

- Fewer than one percent of people living with HIV are “elite controllers” (i.e. people who can spontaneously control HIV viral load without antiretroviral therapy) (1, 2).
- The ability of elite controllers to control their infection is likely due to genetics and a potent HIV-specific immunologic response (3–8).
- Elite controllers develop antibodies to HIV but have extremely low-level or undetectable viral loads, so there is a risk that their HIV infection may be misdiagnosed (9, 10). However, there are no testing algorithms specific to elite controllers (11, 12).
- While elite controllers are able to control their HIV infection, they continue to experience ongoing inflammation, decreases in CD4+ T cells, inflammation-associated cardiovascular disease and high rates of cancer, which suggest that their natural ability to control the virus over the long term may be coming at an immunologic and clinical cost (13).
- When managing elite controllers, clinicians should consider the potential benefits of antiretroviral therapy in reducing inflammation, maintaining CD4+ T cell levels and improving other health outcomes (14).

## References

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## ! The Issue and Why It's Important

Elite controllers are a group of people living with HIV who spontaneously control HIV viral load below the limit of detection for long periods of time in the absence of antiretroviral therapy (15). Elite controllers (also known as elite suppressors) (13) are different from other people with HIV whose disease may progress more slowly (commonly known as long-term nonprogressors, slow progressors, long-term survivors, and nonprogressors) (13), in that their viral load is below the limit of detection over a continuous period of time. Elite controllers have longer AIDS-free intervals as well as improved survival, and more favorable clinical outcomes compared even with viremic controllers with plasma HIV RNA levels of 50–2000 copies/ml (16). This review is focused specifically on elite controllers.

It is important to understand the mechanisms underlying elite control of HIV – particularly in those individuals who have undetectable virus AND normal CD4 counts for at least 10 years – because it may represent a natural model for a “functional cure” (i.e. long term control of viral replication and remission from symptoms of HIV infection in the absence of antiretroviral therapy) (13, 17). The exact mechanisms of elite control remain unclear (18), although it is now believed that host response, including CD4 and CD8 T cell-specific immune response (5, 6), as well as HLA Class I alleles (1, 3, 4), are likely the main mechanisms of control (7, 17, 18), rather than infection by defective virus (2, 17, 18). On the other hand, some researchers suggest that the elite controller phenotype is probably a multifactorial phenomenon (19, 20). A combination of good, anti-HIV host genetics along with infection by an HIV strain with weak replicative capacity may be necessary for elite suppression, whereas only one of these may lead to slow progression and viremia (19, 21).

It is also important to consider the most effective clinical management of elite controllers because, while they can control HIV replication, they have evidence of:

- ongoing inflammation, CD4+ T cell depletion, and perhaps even inflammation-associated cardiovascular disease, which suggests that their natural long-term virologic control may be coming at an immunologic and clinical cost (13).
- abnormal levels of immune activation (22) and/or defects in hematopoietic and thymic tissue regeneration (20, 23, 24), which might be associated with other disease sequelae such as increased carotid atherosclerosis (20, 25).
- high risk of some forms of cancers (26, 27), which suggests that virally silent HIV infection may still foster carcinogenesis (26).

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Elite controllers who are co-infected with hepatitis C may be at particular risk of poor health outcomes. A U.S. study looking at the effect of hepatitis C co-infection on the risk of complications and disease progression found that hepatitis C co-infection does not directly affect HIV replication dynamics or natural history, but it may act synergistically with HIV to produce a greater number of associated complications such as cancer, organ failure, cardiovascular complications, and cirrhosis (28). In fact, elite controllers co-infected with hepatitis C were almost five times more likely to develop such complications compared to their peers who were HIV mono-infected (28). In a recent Spanish study, hepatitis C co-infection was the main factor associated with hepatic and extrahepatic non-AIDS-defining events in elite controllers (29).

## What We Found

### Definition of elite controller

Exact definition of elite control varies from study to study, but most researchers agree that an elite controller has at least three consecutive undetectable HIV-RNA measurements for  $\geq 12$  months in the absence of antiretroviral treatment (18) or undetectable viral loads on at least 90% of measurements over 10 years (2, 15). In other words, the ability to not only achieve undetectable viral loads, but to sustain them differentiates elite controller from others living with HIV (18).

### Prevalence of elite controllers

Elite controllers are rare. Among people with HIV-1, estimated prevalence ranges from 0.15 to 1.5% (16, 30–34). These prevalence estimates are based on data from HIV-positive cohorts within the U.S and Europe (18). Very little is known about the prevalence of elite controllers in Sub-Saharan Africa and Asia (18). The prevalence estimates for those with HIV-1 vary because cut-offs for viral load and time period of follow-up differ depending on the definition of elite control (35). Most definitions classify about 1% of people living with HIV-1 as elite controllers (1, 2).

Among people with HIV-2, the prevalence of elite controllers appears to be much higher than in those with HIV-1 (36). The only identified study of elite control among people living with HIV-2 was conducted in France with a cohort of 749 patients, 8.8% of whom had an undetectable viral load without receiving antiretroviral therapy (36). HIV-2 causes a reduced pathogenic infection with a lower risk of disease progression and transmissibility than HIV-1.

Among elite controllers, there are no consistent demographic patterns (i.e. gender, race) and no differences between controllers and non-controllers in modes of HIV transmission (16, 18). In genetic

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studies, elite controllers have high levels of protective HLA alleles (1).

## Diagnostic testing in elite controllers

Elite controllers develop antibodies to HIV but have extremely low-level or undetectable viral loads without antiretroviral therapy. The lack of a detectable viral load by nucleic acid test (NAT) in an individual positive by serological screening may indicate elite control (1, 37).

Because of these unusual circumstances, there is a risk that the HIV infection may be misdiagnosed (9, 10). However, we were unable to identify any testing algorithms specifically developed for elite controllers (11, 12).

Would it be possible to detect infection in elite controllers in other ways? A study examining to what extent elite controllers also control infection of the central nervous system found that HIV RNA could not be detected in cerebrospinal fluid in most elite controllers using the highly sensitive single-copy assay that allows for HIV RNA quantification down to less than one copy per millilitre (38). When detected with such an extremely sensitive assay, HIV RNA was at significantly lower frequencies and concentrations in the cerebrospinal fluid than in plasma: 19% vs. 54% (38).

Issues related to diagnostic testing in elite controllers can also affect incidence estimates. This estimation, using “incidence assays” that distinguish “recent” from “nonrecent” infection, is based on the assumption that a high prevalence of “recent” infection indicates a high incidence (39). However, incidence assays also tend to produce substantial “false-recent” results (39) and, among elite controllers, there is a high occurrence of “false-recent” rates when estimating HIV incidence from cross-sectional surveys (40). The “false-recent” rates among elite controller specimens is high for all assays, ranging from 13% to 48%, with an average of 25% (39). The introduction of a low viral load threshold provides crucial improvements in “recent infection testing algorithms” (40).

## Recommended clinical management of elite controllers

The durability of HIV control in elite controllers varies, but several epidemiological studies have shown that the spontaneous control of HIV replication can last for extremely long periods of time (i.e. more than 30 years), although loss of immune control is observed in some of these individuals (20).

The most common definitions of elite controllers are based solely on virological criteria, which do not exclude individuals who, despite having undetectable viral load, experience a progressive drop in

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CD4+ T cells and develop AIDS-defining clinical events (20). This progression to AIDS in the presence of undetectable HIV replication is one of the most unexpected findings in elite controllers and its etiology remains unclear (20).

There is also anecdotal evidence that elite controller status does not prevent the risk of super-infection and its clinical consequences such as acute retroviral syndrome following super-infection and immuno-virological progression thereafter (41).

Although clinical data are limited, they suggest that elite controllers may be at heightened risk of illnesses that are not traditionally considered to be HIV-related, including cardiovascular disease (14) and cancer (26, 27). Therefore, guidelines for detecting cardiovascular diseases and guidelines for cancer screening in noncontroller HIV-infected patients should be applied to elite controllers (26).

Would elite controllers benefit from antiretroviral therapy? Initiation of antiretroviral therapy in elite controllers remains controversial. Because of the small number of elite controllers, their long-term success in controlling viral replication, and clinician and/or patient reluctance to start therapy (1), a large, randomised trial of antiretroviral therapy in elite controllers with clinical endpoints is virtually impossible (14).

At this time, the European AIDS Clinical Society Guidelines provide no specific recommendations about treating elite controllers (42). However, in 2016, the U.S. panel of the International Antiviral Society recommended initiating treatment for those who have persistent undetectable viral load without antiretroviral therapy and who have declining CD4 cell counts (43).

Given the clear benefit of antiretroviral therapy regardless of CD4 count, the U.S. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV discourage delaying treatment after initial diagnosis to see if a patient becomes an elite controller (44). As ongoing HIV replication occurs even in elite controllers, antiretroviral therapy is clearly recommended for controllers with evidence of HIV disease progression, as defined by declining CD4 counts or development of HIV-related complications (44).

Although it is unclear whether the potential immunologic benefit of antiretroviral therapy in elite controllers outweighs potential drug toxicity and results in clinical benefit (44), the guidelines state that: there is a clear theoretical rationale for prescribing antiretroviral therapy to elite controllers even in the absence of detectable viral load; and, if antiretroviral therapy is withheld, elite controllers should be followed closely, as some may experience CD4 cell decline, loss of viral control, or complications related to HIV infection (44).

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Elite controllers may benefit from antiretroviral therapy because they have higher levels of immune activation and an increased risk of cardiovascular disease and hospitalization than individuals who achieve virologic suppression with antiretroviral therapy (32, 45). A study comparing health outcomes of these two groups found that elite control was associated with higher rates of cardiovascular, all-cause, and psychiatric hospitalizations (32). Interestingly, the same author in a different study found a trend toward fewer hospitalizations among elite controllers compared to those with HIV RNA <2,000 copies/ml, but this study was not adequately powered to detect a difference in hospitalization rates between elite controllers and subjects with medically controlled HIV (34).

A recent pilot study analyzed the extent to which HIV controllers (including a 25% subset of elite controllers) who have progressive CD4+ T cell loss benefit from antiretroviral therapy (22). It found that antiretroviral therapy for 24 weeks was safe and well-tolerated, and it led to significant decreases in: ultrasensitive plasma and rectal HIV RNA (even among elite controllers who had undetectable plasma HIV RNA levels at baseline), HIV antibody levels, and markers of immune activation/dysfunction in blood and gut. These reductions were similar in the subset of elite controllers (22). These findings confirm that HIV replication persists in controllers and contributes to a chronic inflammatory state (22).

In another study, the size of the pool of CD4+ T cells harboring infectious HIV in elite controllers diminished significantly after initiation of antiretroviral therapy and rebounded to baseline upon its cessation (46). The CD4+ T cell reconstitution after antiretroviral therapy initiation suggests that it may be detrimental to delay initiation of therapy until elite controllers experience a decline in CD4+ T cells (14).

In a very recent study of HIV controllers – of whom 37% were elite controllers with viral load <40 copies/ml, the AIDS Clinical Trials Group investigated the effect of antiretroviral therapy on HIV suppression, viral reservoir, immune activation, markers of inflammation, and quality of life (47). One year of antiretroviral therapy reduced T cell activation and markers of immune exhaustion in HIV controllers, in some cases with further decreases after two years (47). Antiretroviral therapy was well tolerated and did not adversely affect controller status when discontinued (47). The authors concluded that these results support the use antiretroviral therapy in the clinical management of HIV controllers (47). Given these findings, clinicians should consider potential benefits of antiretroviral therapy when deciding whether to initiate treatment in asymptomatic elite controllers (14).

To assist clinicians, researchers have proposed a baseline clinical score that classifies elite controllers according to risk of disease progression (33). This score could be instrumental in informing clinical decisions (33).

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## Factors That May Impact Local Applicability

Studies included in this review have been conducted in high-income settings. Because of similar HIV epidemics, antiretroviral therapy options, and similar incidence and mechanisms of HIV elite control, the review findings are highly relevant and transferable to the Canadian context.

## What We Did

We searched Medline using text term Elite Control\*. Reference lists of identified review articles were also searched. Additionally, we conducted searches on Google and Google Scholar using terms HIV and Elite Controller(s). Searches were conducted on June 18, 2018 and results were limited to English language articles published from 2008 to present. The search yielded 420 references from which 47 studies were included.

### Rapid Response: Evidence into Action

The OHTN Rapid Response Service offers quick access to research evidence to help inform decision making, service delivery and advocacy. In response to a question from the field, the Rapid Response Team reviews the scientific and grey literature, consults with experts, and prepares a brief fact sheet summarizing the current evidence and its implications for policy and practice.

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