Characterisation of long-term non-progression of HIV-1 infection after seroconversion: a cohort study

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Summary

Background Some individuals remain AIDS-free with a high and stable CD4 cell count without antiretroviral therapy (ART) for many years. We estimated long-term progression-free survival after HIV seroconversion and aimed to identify factors associated with loss of long-term non-progression (LTNP) status.

Methods For this cohort study, we used data for individuals with well-estimated dates of HIV-1 seroconversion from the CASCADE Collaboration a network of 28 HIV seroconverter cohort studies in Europe, Australia, Canada, and sub-Saharan Africa. The first cohort began enrolling patients in 1979, and for this analysis we used data pooled in May 1, 2011. We defined non-progression as being HIV-positive without AIDS, ART-naive, and with CD4 counts of 500 cells per μL or higher. We defined LTNP as non-progression during the first 10 years after seroconversion. We used longitudinal methods to characterise LTNP.

Findings Of the 4979 HIV seroconverters in our dataset, 3708 (75%) were men. Median time to progression was 2.07 years (95% CI 1.96–2.17), giving estimated progression-free survivals of 18.4% (17.2–19.6) 5 years, 4.0% (3.6–4.5) 10 years, and 1.4% (0.9–1.5) 15 years after seroconversion. The rate of progression did not change beyond 10 years after seroconversion (0.28 [95%CI 0.26–0.31] per person-year at 10 years after seroconversion, 0.24 [0.19–0.29] per person-year at 15 years, and 0.18 [0.10–0.33] per person-year at 20 years). At 10 years since HIV seroconversion, 283 individuals had LTNP, of whom 202 subsequently lost this status (median time to loss of status 2.49 years [2.05–2.92]). In univariable analyses, loss of LTNP status was associated with CD4 cell count at 10 years after seroconversion (p=0.0001) and HIV RNA load at 10 years after seroconversion (p=0.005), but not age (p=0.544), mode of infection (p=0.676), or calendar year of seroconversion (p=0.397). In the multivariable analyses, loss of LTNP status was associated with lower CD4 counts at 10 years after seroconversion (p<0.0001) and HIV RNA load at 10 years after seroconversion (p=0.005), but not age (p=0.544), mode of infection (p=0.621), sex (p=0.676), or calendar year of seroconversion (p=0.397). In the multivariable analyses, loss of LTNP status was associated with lower CD4 counts at 10 years after seroconversion (p=0.0001).

Interpretation Progression-free survival is rare. Most individuals with LTNP eventually lose immunological and clinical control of HIV infection eventually.

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Introduction Before the advent of combination antiretroviral treatment (ART) in 1996, median time from primary HIV infection to the development of AIDS ranged from 5 years to 11 years.1 With widespread use of combination ART, this period has lengthened substantially. Some individuals remain AIDS-free with a high and stable CD4 cell count without ART for many years.2 In the mid-1990s, much research focus was on studying such individuals with long-term non-progression (LTNP). Since viral load measurements became available,3 this interest has shifted to individuals who were able to naturally suppress the virus (known as HIV-controllers or elite controllers).4 Findings from basic science studies of biological samples from these patients might yield important information about the correlates of control of infection—this information could be beneficial for the development of therapeutic vaccines.5

Studies of LTNP are difficult to compare because of heterogeneity in the definitions of non-progression, study design, and lengths of follow-up.6–10 Moreover, these studies are often limited by small sample size and missing information about date of seroconversion. Additionally, LTNP has generally been established cross-sectionally at a fixed time (eg, at 8 years after infection).11 Some researchers have suggested some people with LTNP have slow progression;12 these people eventually have disease progression rather than being a distinct subgroup able to naturally control the development of HIV infection.12 Moreover, how rare or common non-progression is beyond 10 years after infection is unknown, as is whether individuals with LTNP have no signs of HIV disease progression with continued follow-up.13

The CASCADE Collaboration is, to our knowledge, one of the largest groups of HIV-positive individuals worldwide with known dates of HIV seroconversion, of diverse risk groups, and with long (>10 years) follow-up. As such, the study provides a unique opportunity to study LTNP. We therefore examined the probability of progression-free
Baseline characteristics

Table 1: and HIV RNA measurements in the fi rst 6 months after HIV seroconversion. ¶Missing values: 1040 for total study population and 87 for individuals with long-term non-progression. ‡Several European countries and Canada. §Excludes CD4 cell count measurements for cohort censored. †Mixed route (ie, sex between men and injection drug use; injection drug use and heterosexual contact) or fi rst CD4 cell count measurement 6 months or more after seroconversion (whichever was later) until event or censoring. LTNP=long-term non-progression. *Since cohort enrolment population (N=4979) and subsequently rebound,2 we excluded those with CD4 cell count measurements 6 months or more after seroconversion, of which at least one was in the fi rst 10 years after seroconversion. The estimated date of seroconversion had to be at least 10 years before the administrative censoring date of each individual cohort to allow for potential follow-up beyond 10 years.

Methods
Study population
Concerted action on seroconversion to AIDS and death in Europe (CASCADE) is a collaboration within EuroCoord), a network of 28 HIV-1 seroconverter cohort studies in Europe, Australia, Canada, and sub-Saharan Africa. All collaborating cohorts received approval from their regulatory or national ethics review boards (appendix). Details of CASCADE are described elsewhere." Briefly, CASCADE data comprise 25 629 HIV-positive individuals who had their seroconversion date estimated by the midpoint between a last negative and first positive test separated by a maximum of 3 years (n=21 670 [85%]), the date of laboratory evidence of seroconversion (n=3 231 [13%]), the date of seroconversion illness together with negative and positive tests separated by a maximum of 3 years (n=522 [2%]), or the most likely date that infected factor VIII concentrate infusion for men with haemophilia was given (n=206 [1%]; we used a back-calculation method to estimate the time the infected blood product was used). The fi rst cohort began enrolling patients in 1979, and for this analysis we used data pooled in May 1, 2011.

For these analyses, we included individuals aged 15 years or older at seroconversion who had at least two CD4 cell count measurements 6 months or more after seroconversion, of which at least one was in the fi rst 10 years after seroconversion. The estimated date of seroconversion had to be at least 10 years before the administrative censoring date of each individual cohort to allow for potential follow-up beyond 10 years.

Definition of long-term non-progression
We defined non-progression as being HIV-positive and AIDS-free, ART-naive, and never having a CD4 count below 500 cells per μL. We deﬁned the end of non-progression status as ART initiation, development of an AIDS event, or fi rst measurement of a CD4 count below 500 cells per μL, whichever occurred fi rst. Because CD4 counts might drop sharply soon after seroconversion and subsequently rebound,2 we excluded those measured in the fi rst 6 months after HIV seroconversion. We defi ned LTNP as non-progression during the fi rst 10 years after seroconversion. AIDS diagnosis was based on the Centers for Disease Control revised case deﬁ nition.3"n

Statistical analyses
We calculated follow-up from HIV seroconversion until the date of event or censoring. Individuals were included in the risk set from the later date of cohort enrolment or fi rst CD4 cell count measurement 6 months or more after seroconversion. We censored follow-up at the date when individuals were last assessed for CD4 cell count or ART,

For more on EuroCoord see www.EuroCoord.net
whichever occurred first. We used Kaplan-Meier methods to estimate the probability of progression-free survival in all individuals and in those who were free of progression at 10 years after seroconversion. To investigate trends in the rate of loss of non-progression status, we estimated hazard rates over time since seroconversion with Poisson regression. Restricted cubic splines were used to allow for smoothly varying trends of the hazard over time. We used a Cox proportional hazards model to identify determinants associated with loss of LTNP status beyond 10 years. Factors considered were age at seroconversion, mode of infection, sex, calendar year of seroconversion, baseline CD4 cell count (first measurement between 6 months and 3 years after HIV seroconversion), lowest CD4 cell count in the first 10 years after seroconversion, CD4 cell count at 10 years from HIV seroconversion (or the latest in the preceding 3 years), baseline HIV RNA load (first measurement between 6 months and 3 years after HIV seroconversion), and HIV RNA load at 10 years of HIV seroconversion (or the latest in the preceding 3 years). We used restricted cubic splines to model the effect of CD4 cell count and HIV RNA. We imputed missing HIV RNA values and values below the detection limit using multiple imputation techniques (appendix). We imputed missing mode of infection (four individuals) at random using the distribution of the corresponding variable. All $p$ values were based on null hypotheses against two-sided alternatives. We regarded $p$ values less than 0.05 as statistically significant.

The robustness of the estimated progression-free survival and retention of LTNP status was checked with sensitivity analyses with respect to the role of CD4 count below 500 cells per μL in the definition of non-progression. We did three separate sensitivity analyses. First, we estimated the time when the CD4 count would have dropped below 500 cells per μL on the basis of individual CD4 slopes (which were based on CD4 counts measured before ART initiation only). We obtained these estimates by fitting a linear regression model for each individual with time as the only covariate. We applied a square-root transformation to the CD4 cell count to better normalise the marker distribution as previously described. We applied left truncation by including individuals in the risk set from their first CD4 measurement onwards. Therefore, individuals were excluded from the analysis if the estimated CD4 value was below 500 cells per μL at the moment of the first measurement. Second, with the same method, we required at least four CD4 cell counts to estimate the individual slopes instead of two. Third, we defined progression as two consecutive CD4 counts below 500 cells per μL rather than one. Therefore, individuals had to have at least three CD4 cell counts. We censored follow-up on individuals who did not have two consecutive CD4 counts below 500 cells per μL at the date of the penultimate count. When an individual had two consecutive CD4 counts below 500 cells per μL, we estimated the time to crossing below the 500 cells per μL threshold by interpolation.
between the first count and the previous one, which, by definition, was 500 cells per μL or higher.

We used SPSS (version 19.0), Stata (version 11.2), and R (version 3.0.1) for the analyses.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Most participants were men and the most frequent route of infection was sex between men, followed by sex

### Table 2: Cox proportional hazard analyses of factors associated with of loss of LTNP status in 283 individuals with known dates of HIV-seroconversion identified as having LTNP at 10 years after HIV seroconversion

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
<th>p value</th>
<th>Adjusted HR (95% CI)*</th>
<th>p value</th>
<th>Adjusted HR (95% CI)†</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at seroconversion (per 10-year increase)</td>
<td>0.94 (0.77–1.15)</td>
<td>0.544</td>
<td>1.07 (0.83–1.38)</td>
<td>0.588</td>
<td>1.06 (0.83–1.37)</td>
<td>0.622</td>
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<td>Age at seroconversion (years)</td>
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<td>25–29</td>
<td>0.90 (0.65–1.25)</td>
<td>0.319</td>
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<td>30–34</td>
<td>0.66 (0.42–1.04)</td>
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<tr>
<td>≥35</td>
<td>0.86 (0.55–1.34)</td>
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<tr>
<td>Mode of infection‡</td>
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<td>0.621</td>
<td>0.851</td>
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<td>Sex between men or sex between a man and a woman</td>
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<td>1</td>
<td></td>
<td>1</td>
<td>0.959</td>
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<tr>
<td>Injection-drug use or receipt of contaminated factor VIII concentrate in people with haemophilia</td>
<td>1.08 (0.80–1.44)</td>
<td></td>
<td>1.04 (0.70–1.54)</td>
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<td>0.99 (0.67–1.45)</td>
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<tr>
<td>Sex</td>
<td></td>
<td>0.676</td>
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<tr>
<td>Female</td>
<td>1.07 (0.78–1.46)</td>
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<td>1.29 (0.87–1.72)</td>
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<td>1.22 (0.83–1.79)</td>
<td>0.316</td>
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<td>Calendar year of HIV seroconversion (per year increase)</td>
<td>0.98 (0.95–1.02)</td>
<td>0.397</td>
<td>0.82 (0.49–1.38)</td>
<td>0.449</td>
<td>0.97 (0.92–1.02)</td>
<td>0.254</td>
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<td>Calendar year of HIV seroconversion</td>
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<td>0.719</td>
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<tr>
<td>&lt;1989</td>
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<tr>
<td>1989–1992</td>
<td>0.86 (0.62–1.20)</td>
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<td>1993–1996</td>
<td>0.83 (0.58–1.19)</td>
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<tr>
<td>≥1997</td>
<td>0.80 (0.55–1.18)</td>
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<td>Baseline CD4 count (cells per μL)§</td>
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<td>0.290</td>
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<td>600</td>
<td>1</td>
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<tr>
<td>900</td>
<td>0.80 (0.52–1.23)</td>
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<td>Lowest CD4 count in the first 10 years after seroconversion (cells per μL)§</td>
<td>0.084</td>
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<td>600</td>
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<td></td>
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<tr>
<td>900</td>
<td>0.62 (0.40–0.99)</td>
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<tr>
<td>CD4 count at 10 years of HIV seroconversion (cells per μL)§</td>
<td>&lt;0.0001</td>
<td></td>
<td>&lt;0.0001</td>
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<tr>
<td>600</td>
<td>1</td>
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<tr>
<td>900</td>
<td>0.36 (0.23–0.55)</td>
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<td>0.39 (0.24–0.62)</td>
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<tr>
<td>Baseline HIV RNA (log10 copies per μL)† §</td>
<td>0.090</td>
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<td>3</td>
<td>1</td>
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<tr>
<td>4</td>
<td>1.27 (0.85–1.91)</td>
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<tr>
<td>HIV RNA at 10 years of HIV seroconversion (log10 copies per μL)† §</td>
<td>0.005</td>
<td></td>
<td>0.120</td>
<td>0.009</td>
<td></td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
<td>1.40 (0.92–2.13)</td>
<td></td>
<td>1.24 (0.81–1.86)</td>
<td></td>
<td>1.38 (0.91–2.03)</td>
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</table>

LTNP=long-term non-progression. HR=hazard ratio. *Adjusted for all factors for which adjusted HRs are shown; owing to the strong correlation between the measurements of baseline CD4 count, lowest CD4 count, and CD4 count at 10 years since infection, these three covariates were not included together in the multivariable model; baseline HIV RNA and HIV RNA at 10 years since infection were not included together in the same model. †Adjusted for all factors for which adjusted HRs are shown; CD4 cell count is not included in the model because it is included in the definition of progression; owing to the strong correlation between the measurements baseline HIV RNA and HIV RNA at 10 years since infection these two covariates were not included together in the same model. ‡Missing mode of HIV infection (n=4) and missing HIV RNA values (n=87) were imputed. §HR estimated with restricted cubic splines.

Table 2: Cox proportional hazard analyses of factors associated with of loss of LTNP status in 283 individuals with known dates of HIV-seroconversion identified as having LTNP at 10 years after HIV seroconversion
between men and women, injection drug use, and receipt of contaminated factor VIII concentrate in people with haemophilia (table 1). The median year of HIV seroconversion was 1992 and all included individuals were from high-income countries, except for three individuals who were included in cohorts in Africa (table 1).

4246 individuals progressed within 10 years of HIV infection: 3253 with CD4 counts below 500 cells per μL, 729 started ART, 81 had AIDS event, and 183 had a combination of these signs of progression. The median time to progression was 2·07 years (95% CI 1·96–2·17). The estimated progression-free survival probability at a given time since seroconversion was 18·4% (17·2–19·6) at 5 years, 4·0% (3·6–4·5) at 10 years, 1·4% (0·9–1·5) at 15 years, and 0·3% (0·2–0·6) at 20 years (figure 1).

The rate of progression over time since HIV seroconversion decreased sharply in the first years after seroconversion from 0·45 (0·43–0·48) per person-year in the first year to 0·32 (0·30–0·33) per person-year at 5 years after seroconversion (figure 2). Thereafter, the rate continued to decrease, but slowly, to 0·24 (0·19–0·29) per person-year at 15 years and 0·18 (0·10–0·33) per person-year at 20 years after seroconversion.

After 10 years of HIV infection, 283 individuals were classified as having LTNP (table 1). Of these people with LTNP, 202 lost this status after 10 years of HIV seroconversion: 150 because of decrease in CD4 cell count to below 500 cells per μL, 28 started ART, seven had an AIDS event, and 17 had a combination of these signs of progression. Median time to loss of LTNP status was 2·49 years (95% CI 2·05–2·92; figure 3). The estimated progression-free survival in those with LTNP was 29·6% (23·8–35·6) at 15 years from seroconversion and 8·6% (4·3–14·8) at 20 years from seroconversion.

In univariable analysis the loss of LTNP status was associated with lower CD4 cell count and higher HIV RNA load at 10 years after HIV seroconversion (table 2). In multivariable analysis, the loss of LTNP status was independently associated with a lower CD4 count at 10 years after seroconversion (p=0·0012; table 2). The adjusted hazard of loss of LTNP status decreased with increasing CD4 cell count (p<0·0001; figure 4). Although not statistically significant, the adjusted hazard of loss of LTNP status seemed to increase with increasing HIV RNA at 10 years after HIV seroconversion (p=0·12; figure 4). We detected no associations between loss of LTNP status and age at HIV seroconversion, route of infection, sex, or calendar year of seroconversion. After exclusion of CD4 cell count from the model because it was part of the definition of non-progression, we noted that a higher HIV RNA at 10 years after HIV seroconversion was independently associated with loss of LTNP status (p=0·009; table 2). When we included baseline CD4 cell counts and HIV RNA in the model instead of the values measured at 10 years after seroconversion, we saw no association between loss of LTNP status and HIV RNA (p=0·18) or CD4 cell count (p=0·72).

The CD4 cell count and HIV RNA trajectories for the seven individuals who still qualified as having LTNP at 20 years after HIV seroconversion were heterogeneous with respect to demographic characteristics; six of them were male, all routes of infection were present, age at HIV seroconversion ranged between 19 years and 33 years, and they were enrolled into six different cohorts.
Two of the individuals subsequently lost LTNP status (individuals 4 and 7; figure 5). Individual 1 had an increase in viral load, which might indicate progression. The other four individuals did not have signs of clinical or immunological progression and their viral load remained stable (figure 5).

In the first and third sensitivity analyses, the median duration to progression and the median progression-free survival times after LTNP were very similar (data not shown). In the second sensitivity analyses, the median progression-free survival time increased slightly to 2.87 years (2.69–3.00). The estimated progression-free survival at a given time from seroconversion was slightly higher at 26.3% (24.7–27.8) at 5 years, 6.7% (6.0–7.5) at 10 years, and 2.5% (2.0–3.0) at 15 years. Median progression-free survival time after LTNP was similar to that seen in the main analysis (data not shown).

Discussion In our large cohort study we found that LTNP is rare, with progression-free survival decreasing rapidly, being about 18% 5 years after seroconversion and about 4% 10 years after seroconversion. To the best of our knowledge, our study is the first to report median time from seroconversion to loss of non-progression, which was 2.07 years (IQR 1.14–3.99). By contrast with our findings, cross-sectional estimates of LTNP from other studies have ranged from 0.2% to 22.3%, depending on the definition used (panel).6,7,18,19 Estimation of the prevalence of individuals with LTNP, especially when the date of HIV seroconversion is unknown, might result in the exclusion of people with more rapid progression and, therefore, might lead to an overestimation of the prevalence. In our study, the rate of progression decreased rapidly over the first few years after seroconversion but remained constant beyond 5 years. Although our data lend support to previous suggestions that individuals with LTNP are more likely to represent the end of the tail from a distribution than a distinct subpopulation, we cannot exclude the possibility that some individuals will never have disease progression.6,11,12

Individuals with LTNP at 10 years after seroconversion were heterogeneous in terms of their demographic characteristics and viral load, as were those who remained free of progression for 20 or more years. To identify underlying mechanisms of LTNP, stringent and uniform definition criteria are important because a small change in definition might have a large effect on the apparent outcome.6,8 The criteria we used to define LTNP were stringent with respect to follow-up and CD4 cell counts.1,7

Figure 5: CD4 cell counts (A) and HIV RNA loads (B) in seven individuals who remained progression-free for 20 or more years after HIV seroconversion
(A) Blue dots are values recorded during follow-up, green dots are values recorded after an individual’s follow-up was censored, and red dots are values recorded after an event had taken place (CD4 count <500 cells per µL).
(B) Solid dots are values above the detection limit; circles are values below the detection limit of the HIV RNA test.
The results of retention of LTNP status did not change in the sensitivity analyses, and all analyses substantiated the finding that LTNP is uncommon.

Although the reason for the slow—or absent—progression in people with LTNP is unclear, several factors are likely involved,\textsuperscript{21,22} including infection with an attenuated virus.\textsuperscript{21} However, findings from previous studies also suggest that non-progressors are infected with a pathogenic virus, lending support to the idea that host, rather than viral, factors play a large part in the absence of disease progression.\textsuperscript{23} Host genetic factors such as CCR5Δ32 deletion and heterozygous HLA-B57 alleles have been described.\textsuperscript{24} A genome-wide association study showed five single-nucleotide polymorphisms in class I and III MHC subregions that were associated with LTNP.\textsuperscript{3} Few studies have been done of the immunological variables in people with LTNP, and researchers who did a review of available studies recommended the study of T-cell subsets with proinflammatory and anti-inflammatory properties such as Th17 and regulatory T-cells and their role in the preservation of normal CD4 cell counts in those with LTNP.\textsuperscript{25} Another review showed the effect of heritability of HIV on viral load.\textsuperscript{26} Phylogenetic analysis might, therefore, be of interest to identify any role of heritability of the virus on LTNP.

Only two studies have assessed on the loss of LTNP status by use of data from HIV seroconverters. Findings from a study from San Francisco showed a median time to loss of LTNP status after 10 years of HIV infection of 14 years (95% CI 13.0–14.7), slightly longer than our estimate of 12.5 years (12.1–12.9).\textsuperscript{7} The second study, done in France, showed a time to loss of LTNP status similar to ours, but was estimated after 8 years rather than 10 years since HIV infection.\textsuperscript{8} Older age at HIV seroconversion is associated with more rapid progression to AIDS and death,\textsuperscript{2} as was shown in our study, with age associated with loss of non-progression in the total study population (data not shown). Our findings suggest that once someone had been free of progression for 10 years or longer, age is no longer significantly associated with progression—a finding also seen in the French study.\textsuperscript{26}

The identification of people with LTNP might become challenging in the future if the trend towards earlier initiation of combination ART continues; although the individual benefits of earlier ART remain debatable, treatment guidelines now recognise the possibility that the initiation of ART at a very early time during HIV infection to prevent HIV transmission (so-called treatment as prevention) could have public health benefits.\textsuperscript{27,28} Progression-free survival in our study was low, indicating that, if earlier start of ART is implemented, for most this earlier start will be a few years, which might be short in comparison with the many years of treatment to follow.

An overlap between the LTNP group and HIV-controllers and elite-controllers has been reported.\textsuperscript{18,29} In our study, 30 (21%) of the identified people with LTNP also met the criteria for HIV control, as described in a previous study from CASCADE Collaboration that identified 140 HIV controllers (data not shown).\textsuperscript{30}

Limitations of our study included the fact that all individuals, apart from three, were included in high-income countries and that we were not able to estimate ethnicity-specific progression-free survival. Therefore, our results might not be generalisable to other countries. However, both white and non-white individuals were identified as LTNP, suggesting that the possibility to have LTNP is not restricted to one ethnic group. Also, coding imperfection might have occurred and we cannot rule out residual and unmeasured confounding.

Although lifetime natural control of HIV is unlikely, further studies of host immunity and genetics using biological samples of the few individuals with durable control might help in the development of therapeutic vaccines.
revision of the paper, and supervised the study. All authors approved the final version of the paper.

**Declarations of interest**
We declare no competing interests.

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**References**


