

Natural selection and resistance to HIV

A genotype that lowers susceptibility to HIV extends survival at a time of peak fertility.

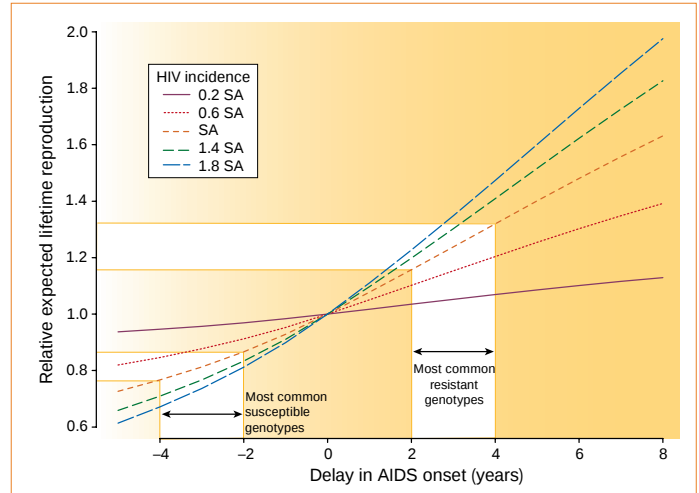
Although infectious disease is assumed to be an important cause of natural selection in humans, strong selection in favour of alleles that confer resistance to disease has been demonstrated only in the case of malaria¹. Here we show that the high prevalence of human immunodeficiency virus (HIV) in some African countries creates conditions for strong natural selection on genetic variants that affect the time between HIV infection and the onset of AIDS. Moreover, a rapid evolution of resistance to AIDS onset is expected in these populations if the current HIV epidemic conditions persist.

In 1999, the prevalence of HIV infection in adults was 20% in South Africa, 36% in Botswana, 25% in Zimbabwe and 20% in Zambia². Assuming that the current incidence of HIV infection and the mortality caused by AIDS do not change, the lifetime risk of dying of AIDS for a boy who was 15 years old in 1999 is over 65% in South Africa and almost 90% in Botswana².

Variant forms of CCR5, a cell-surface receptor for mediator molecules known as chemokines, have been found to affect susceptibility to HIV infection and the period before the onset of AIDS in people carrying alleles for the variant forms. These genetic polymorphisms will be subjected to considerable natural selection because they increase survival time during the period of peak fertility. The HIV-resistant haplotypes that are most common in Africans³ delay post-infection progression to AIDS by 2–4 years and, conversely, common HIV-susceptible haplotypes accelerate AIDS onset by a similar amount.

Figure 1 shows the estimated expected lifetime reproduction relative to the normal genotype as a function of delay in AIDS onset. The 'SA' curve corresponds to the estimated HIV incidence in 1997 in South Africa⁴. The expected lifetime reproduction is roughly 15% greater for genotypes in which AIDS onset is delayed by 2 years, and roughly 30% greater for genotypes that

Figure 1 Expected lifetime reproduction of carriers of CCR5 mutations relative to the normal CCR5 genotype as a function of the period between HIV infection and the onset of AIDS. Curve 'SA' was calculated using HIV-incidence values estimated for a rural district in South Africa⁴; other curves were calculated with all incidence values multiplied by the indicated factor. Calculations are based on 1980 demographic data⁵ (assumed to be before the AIDS epidemic) for South Africa and an exponential survivorship curve for the time until AIDS onset. Mean time to AIDS onset is 7 years for the normal genotype and changes by the times shown for resistant or susceptible genotypes. Further details will be published elsewhere.



delay onset by 4 years. The expected lifetime reproduction of HIV-susceptible (AIDS-accelerating) genotypes is reduced to a comparable extent.

Estimates of the incidence of HIV infection have a high degree of uncertainty, so we have included other curves in Fig. 1, representing different overall incidence levels. The '0.6 SA' curve, for example, corresponds roughly to incidence values estimated for a Ugandan population with a similar prevalence distribution to that for the South African population⁵. The expected lifetime reproduction for this incidence distribution varies from 9% greater than the normal genotype for an onset delay of 2 years, to 19% greater for an onset delay of 4 years.

Table 1 shows the projected evolution of haplotype frequencies and the effect on average time to AIDS onset when these haplotypes are exposed to HIV at South African incidence levels⁴. In 100 years, the frequency of the AIDS-delaying haplotype increases from 0.4 to 0.53 and the average time to onset increases by 1 year.

The selective advantage calculated here is comparable to that of malaria resistance

in heterozygous carriers of the haemoglobin S allele (which is responsible for sickle-cell anaemia in SS homozygotes) in regions where malaria is common. Our estimate of the intensity of selection caused by HIV today is also comparable in magnitude to the 30% advantage conferred by the $\Delta 32$ mutation in CCR5 (a 32-base-pair deletion that leads to loss of the receptor on lymphoid cells) in European populations over the past 700 years⁶. Our results offer some insight into the cause of this selection. Bubonic plague has been proposed to be the selective agent for the $\Delta 32$ mutation⁶. In its worst outbreak, the plague caused 25–35% mortality over much of Europe during the Black Death from 1346 to 1352. The mortality in Africa caused by HIV will rise to at least that level and probably higher.

If heterozygous carriers of this deletion had only partial resistance to plague, selection would have been of roughly the same intensity as in populations with a high prevalence of HIV infection. However, unpublished calculations (by P.S.) show that epidemics of plague persisted for too short a time for a selective advantage of 10–30% to account for the current high frequency of the disease. Instead, heterozygous carriers of the CCR5 mutation would have to have been completely resistant to plague (or to a similar pathogen), which would confer a much greater selective advantage.

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Table 1 Projected changes under HIV-induced selection

Timescale (years)	Resistant-haplotype frequency	Susceptible-haplotype frequency	Average time to AIDS onset (years)
0	0.40	0.20	7.8
20	0.43	0.17	8.1
40	0.46	0.15	8.3
60	0.49	0.13	8.5
80	0.51	0.12	8.6
100	0.53	0.10	8.8

Estimates for African populations were calculated using standard equations for evolution of age-structured populations⁷. Predicted frequencies of haplotypes subjected to constant HIV incidence are shown. Incidence values are those calculated in ref. 4. The initial frequencies correspond to those found earlier³, with the eight most common types being collapsed into three types. The estimated frequency of the 'normal' haplotype remains almost constant at 0.4 and is not shown. The average time between HIV infection and AIDS onset is also calculated.

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Climate change

Increasing shrub abundance in the Arctic

The warming of the Alaskan Arctic during the past 150 years¹ has accelerated over the last three decades² and is expected to increase vegetation productivity in tundra if shrubs become more abundant^{3,4}; indeed, this transition may already be under way according to local plot studies⁵ and remote sensing⁶. Here we present evidence for a widespread increase in shrub abundance over more than 320 km² of Arctic landscape during the past 50 years, based on a comparison of historic and modern aerial photographs. This expansion will alter the partitioning of energy in summer⁷ and the trapping and distribution of snow in winter⁸, as well as increasing the amount of

carbon stored in a region that is believed to be a net source of carbon dioxide⁹.

During oil exploration of the United States Naval Petroleum Reserve no. 4 in northern Alaska in 1948–50, low-altitude oblique photographs of exceptional clarity were taken at thousands of locations between the Brooks Range and the Arctic coast¹⁰. In July of 1999 and 2000, we took photographs at 66 of the same locations spanning an area 400 km (east to west) by 150 km. We analysed pairs of new and old photographs for changes in the three principal deciduous shrubs, dwarf birch (*Betula nana*), willow (*Salix* sp.) and green alder (*Alnus crispa*), and for changes in treeline white spruce (*Picea glauca*) along the southern edge of the study area.

In 36 of the 66 repeat photo-pairs, we found distinctive and, in some cases, dramatic increases in the height and diameter

of individual shrubs, in-filling of areas that had only had a scattering of shrubs in 1948–50, and expansion of shrubs into previously shrub-free areas (Figs 1, 2). At tree-line sites, there was a marked increase in the extent and density of the spruce forest (Fig. 2). In some cases, shrub-dominated vegetation that covered about 10% of the landscape in 1948–50 had doubled by 2000. In the 30 photo-pairs in which the amount of deciduous shrubs had not increased, there was no detectable reduction in shrub abundance either.

The increase in shrub abundance appears to have been mainly the result of the growth and expansion of alder, perhaps partly because dark-coloured alder are the most conspicuous shrubs (Fig. 1). However, in several photographs ($n=4$), birch and willow were also seen to have increased in abundance. All three species belong to the same functional group and respond to experimental warming and fertilization in a positive manner⁵. This indicates that the abundance of the smaller dispersed birch and willow found throughout tussock tundra may also be increasing, and so our detection of change could be conservative. These smaller shrubs comprise most of the shrub biomass in the study area.

Our study area is in a location where human and natural disturbances (leading to successional changes) are minimal, so we attribute much of the increase in the abundance of shrubs to the recent change in climate. During the Early Holocene, warming in the Alaskan Arctic was accompanied by one or more large-scale shrub invasions¹¹, and today shrub abundance increases along latitudinal temperature gradients¹². These findings, combined with our observations, show that the vegetation of the region is able to respond to changes in climate, perhaps rapidly. The extensive peat deposits¹³ are evidence that the region has been an important sink for global carbon in the geological past. The increased primary production inferred from our photographic analysis could be a significant contributor to changes in the high-latitude carbon budget, as well as contributing to important changes in the exchange of surface energy.

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Figure 1 The Ayiyak River (N68° 53', W152° 31'), showing an increase in the density of shrub patches, the growth of individual shrubs and an expansion of shrubs into areas that were previously shrub-free. A and B denote the same locations in the old and new photographs.

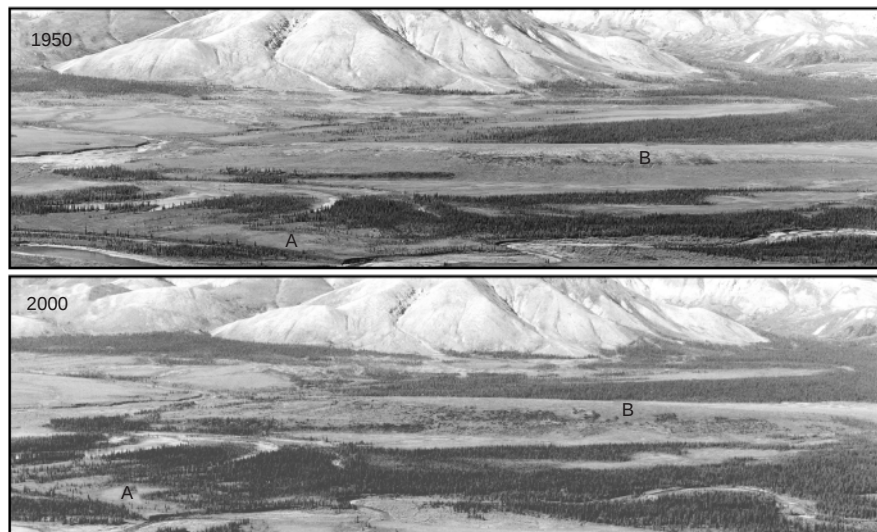
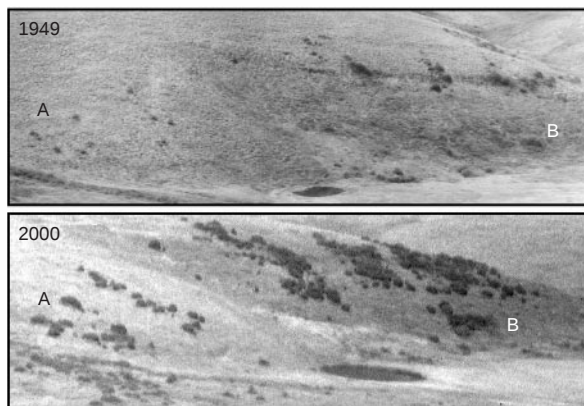


Figure 2 The Kuguruk River (N68° 06', W161° 31'), showing in-filling of spruce stands (A) and increased abundance of shrubs in the middle ground (B); A and B denote the same locations in the old and new photographs.