Under pressure

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We've all heard about resistance and "drug resistant" virus, but just how does HIV become resistant to treatment? Why is it that missing doses of antiretroviral [1]A medication or other substance which is active against retroviruses such as HIV. drugs can make HIV resistant to those drugs? Shouldn't it be the other way around? This month's Backgrounder explores the science behind resistance.

This story begins on New Year's Eve, December 31, 1831. A young English naturalist, Charles Darwin, watches from the deck of the HMS Beagle as the ship sets sail from Plymouth on a five-year voyage of discovery.

The purpose of the trip is not science, but geography. The commander of the ship, Robert Fitzroy, has been commissioned by the British navy to chart the coast of South America. Darwin, just 22 years old, has accepted the unpaid position of naturalist on the journey against his father's wishes. He wants to see the world.

In the years ahead, Darwin will indeed see the world and, while observing finches in the Galapagos Islands, he will make one of the most important scientific discoveries of all time: the theory of evolution.

One of the key concepts in Darwin's theory is that of **natural selection**, the process by which living things gradually change into new and better-adapted forms due to tiny random mutations that make them more fit to survive in their environment.

The changes happen randomly, but natural selection enforces order on the process over time. Within every species there is a degree of genetic variety brought on by the random mutations that happen during reproduction. A process called **selective pressure** ensures that the portion of the population with the better characteristics are more likely to survive and pass their genes [2]The most basic unit of genetic information. on to successive generations.

Usually, selective pressure operates over very long time spans, but sometimes it can cause a species to change very quickly, such as in the case of Britain's peppered moth, which changed its colour from grey to black within a few years during the Industrial Revolution.

Peppered moths spend much of their time perched on tree trunks where they are camouflaged from predators. As the rapid growth of industry covered Britain's trees with soot, the darker-coloured moths were better camouflaged, and the species underwent rapid evolution.

Natural selection in HIV

By the same process, and at even greater speed, HIV is constantly mutating in random ways. In someone with unsuppressed HIV infection, as many as 10 billion new virus particles are formed every day — more than the population of humans on Earth. Many of these new **virions** (a virion is a virus in its infective form, outside a host cell) contain small genetic differences from their forebears — in fact, it's estimated that in people who are not suppressing their HIV infection, every possible genetic mutation is generated every day.

Every living thing has a genetic code stored on genetic material inside its cells. In humans and most living things this genetic material is called DNA. In **retroviruses** like HIV, it is called **RNA** (ribonucleic acid), a long string of **nucleotides** which acts like a computer program with all the instructions the virus needs to reproduce.

Because viruses are extremely simple — albeit clever — organisms, even tiny changes in the viral RNA code can result in quite substantial mutations in the virus. Fortunately, most of these mutated viruses are **non-viable**, that is they are unable to survive or replicate effectively. But many mutations do result in viable viruses that can continue to invade CD4 cells and make new copies of themselves.

In the absence of treatment, the fittest and strongest viral type will eventually dominate, but when treatments are added into the picture, they can exert selective pressure on the virus, which encourages mutations leading to drug

resistance.
Antiretroviral drugs work by preventing the virus from making copies of itself. This is done by suppressing one of the viral **enzymes** (small proteins) that HIV needs in order to replicate. Different classes of drugs suppress different enzymes — either**reverse transcriptase** or **protease** in the case of the drugs we use now.

But in order to block the enzyme, the drug must first **bind** (attach itself) to the virus, and to do this it needs to locate specific genetic markers on the virus' surface. If the virus has mutated in a way that changes the specific markers that a specific drug is designed to look for, the drug won't bind to that virus.

Not every viral mutation will result in resistance. It's only when a specific pattern of changes happen at specific **codons** (locations along the single strand of RNA that carries the virus' genetic code) that resistance occurs.

By taking several drugs in combination, the ability of HIV to avoid detection in this way is reduced, because one of the other drugs in the combination will usually find and destroy the virus that the first drug has missed.

Suppressing viral load [3]A measurement of the quantity of HIV RNA in the blood. Viral load blood test results are expressed as the number of copies (of HIV) per milliliter of blood plasma. to very low levels using several drugs at the same time significantly reduces the number of mutations that occur each day and the likelihood that a viable resistant virus will emerge. This is how some people with HIV are able to take the same combination of drugs for several years without developing resistance.

But whenever the virus' replication is not suppressed adequately, the chances of developing resistance increase. This can happen if the drugs are not effective enough in the first place to reduce the viral load to low levels, or when missing doses exerts selective pressure on the virus.

How missed doses can create resistance

One of the most important messages that HIV-positive people have heard over and over again is the importance of taking every dose on time, every time. This may sound like a scam cooked up by the drug companies to increase sales of their product, but in fact there's a very good reason for it.

Missed doses not only create an opportunity for the virus to multiply, increasing the viral population, but they can also apply selective pressure which encourages HIV to mutate into resistant forms.

Darwin discovered that the finches on different islands in the Galapagos were uniquely adapted to fit a specific ecological niche that varied from island to island. On one island Darwin observed that the finches ate insects while on another they survived on nectar from flowering plants. Despite the physical similarity between the birds, Darwin could see that they had started to evolve in different directions and that over a long period of time their particular ecological niche would dictate their physical characteristics.

Taking nectar from flowers calls for a long, pointed beak and tongue, while insect eaters need speed, agility and good eyesight. Darwin discovered that the relative abundance of flowering plants on one island applied selective pressure to the birds there, favouring the survival of otherwise random mutations towards longer beaks.

The same thing happens with HIV: the fittest virus for the environment tends to become dominant. After allowing HIV an opportunity to multiply by missing a treatment dose, the next dose applies selective pressure that favours genetic mutations — even in a tiny number of individual viruses — which are resistant to the particular treatments being taken.

Resistance to treatment is usually not absolute, so the newly mutated virus may still be suppressed by treatment, but the suppression will be less effective. Even if viral load returns to undetectable levels, the virus has inched a tiny bit closer towards becoming resistant to treatment.

Over time the effect is cumulative: tiny mutations in HIV's genetic code, in the right conditions, act as a kind of built-in genetic program that is designed, not just for HIV but for every living organism, to ensure the long-term survival of the species.

"In the survival of favoured individuals and races, during the constantly-recurring struggle for existence, we see a powerful and ever-acting form of selection," Darwin wrote.

Like so much in nature, natural selection is not just powerful and ever-acting, but exquisitely beautiful in its simplicity and a deeply intertwined part of our own struggle against HIV.

- drug resistance

Links:
[1] http://napwa.org.au/glossary/term/122
[2] http://napwa.org.au/glossary/term/126
[3] http://napwa.org.au/glossary/term/416