# Can Multiple Sclerosis be treated with HIV drugs?

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**Abstract**

In 2015, BBC News posted a case of a patient with Multiple Sclerosis (MS) whose symptoms remarkably improved during a 28-day-medication of Human Immunodeficiency Virus (HIV) anti-retroviral therapy; Multiple Sclerosis symptoms reoccurred after the end of the treatment. It is unknown what causes Multiple Sclerosis, but there are theories that include virus infection. Only a few case reports include AIDS patients with Multiple Sclerosis at the same time. If Multiple Sclerosis is linked to HIV, then HIV antiretroviral therapies could be the key to find the cure for Multiple Sclerosis. INSPIRE is a clinical trial using the HIV anti-retroviral drug Raltegravir, in order to treat Multiple Sclerosis patients who are not infected with HIV. Results of that trial combined with improved diagnostic techniques will assist in finding sooner the treatment of Multiple Sclerosis.

**Introduction: An unusual case**

A 36-year-old woman from East Sussex was diagnosed with Multiple Sclerosis at the age of 28. Ever since, she has been unable to walk without wheelchair-assistance. However, as documented by BBC News, something unique happened in 2014: Shana Pezaro started walking again with the aid of crutches. What happened is that, after fearing she may have contracted HIV, Shana Pezaro was administered emergency HIV drug treatment and her MS symptoms improved dramatically, resulting in her being able to walk again (Multiple Sclerosis Society, 2015).

Are HIV and MS actually connected, or did Shana Pezaro walk as part of a 'miracle cure'? Professor Julian Gold, from the Prince of Wales Hospital in Sydney, after seeing a video of that patient climbing stairs, decided to undertake a clinical trial to examine whether MS in the UK could be treated with HIV drug therapy (BBC News, 2015).

**Multiple Sclerosis background information**

General characteristics

MS is a disease affecting an estimated number of more than 2,300,000 people in the world (Multiple Sclerosis International Federation, 2013). According to Multiple Sclerosis International Federation (2015), the most common MS symptoms include fatigue, pain, bladder and sexual dysfunction, movement and coordination difficulty, visual problems, as well as cognition and emotional changes. Among characteristics of MS, the average age of disease onset is 30 years, which in many cases can develop progressive accumulation to disability, reaching the point of permanent use of wheelchair in later stages of the disease (25 years after diagnosis) (Dendrou *et al.*, 2015; Dendrou *et al.*, 2016). Nevertheless, the course of the disease can be developed differently and hence there are different types of MS. The majority (85 percent) of MS patients develop relapsing-remitting MS, which is characterised by unpredictable attacks or exacerbations. The second most frequent type is the progressive MS: people who are diagnosed with primary progressive MS or secondary progressive MS constitute around the 10 percent of MS cases; both kinds are characterised by slow steadily worsening MS symptoms. The least common type of MS (5 percent) is the progressive relapsing MS, in which the disease steadily worsens with occasional relapses (Multiple Sclerosis International Federation, 2015).

With regards to MS, the disease is not fully understood yet. At the moment, there are some medications that can be applied in earlier stages of the disease, relieving only its symptoms. A cure for MS that can be shown to be effective at later stages of disability is not available (Nissen *et al.*, 2013; Dendrou *et al.*, 2016). This implies that, because of the complexity of this disease, the potential therapy will target a combination of immunological and neurological pathways (Dendrou *et al.*, 2016).

Classification of the disease

Firstly, the concept of autoimmunity should be explained in order to understand the pathology of MS. The immune system can be described ‘like a highly trained army’ which

'has evolved to recognize and destroy foreign invading forces' (Male *et al.*, 2012, pp. 323). A particular type of cell of our immune system is called T-cells. Focusing on one type of T-cells, T-helper (Th) cells, widely known as $CD4^+$ cells, are part of this 'highly trained army' that recognise foreign material. Despite the presence of the 'patrol mechanisms' of the immune system, sometimes this kind of 'recognition fails having as a result "friendly fire" against the body's own tissue' (Male *et al.*, 2012, pp. 323). In that case, someone's autoreactive T-cells are responsible for attacking the body itself, as it is mistakenly recognised as an enemy.

Returning to understanding its pathology (functional manifestations), MS is a chronic autoimmune disease of the central nervous system (CNS), which is constituted by the brain and the spinal cord. This disease is caused by malfunctioning T-cells, which wrongly identify the myelin sheaths around the axons of the CNS as a threat, ordering their destruction. Myelin sheaths insulate the nerve fibres and enable faster transmission of impulses; the destruction of these sheaths is called demyelination. Demyelination causes the creation of areas known as plaques or lesions in the white and grey matter, tissues of the brain and the spinal cord related to coordination between nerves and the CNS (Figure 1). As a consequence, the formation of lesions can be responsible for several neurological abnormalities and clinical disabilities, after gradual loss of axons and neurons (Nissen *et al.*, 2013; González- Duarte *et al.*, 2011; McKay *et al.*, 2015; Dendrou *et al.*, 2015).

Suspected cause of the disease

As far as MS etiology is concerned, what causes MS remains enigmatic. However, it is agreed that MS is a multifactorial disease of a contributing combination of viral, genetic and environmental causes (McKay *et al.*, 2015). The environmental suggested causes consist of cigarette smoking, lack of vitamin D and circadian disruption (Dendrou *et al.*, 2015). As for the viral causality, several viruses have been suggested to be associated with MS. These viruses include Herpes Viruses, specifically the Human Herpes Virus type 6 (HHV-6) and the Epstein-Barr Virus (EBV) (Kakalacheva *et al.*, 2016). Besides Herpes Viruses, Human Endogenous Retroviruses (HERVs) are implicated to MS, namely the MS-associated Retrovirus (MSRV) and the W family of HERVs (HERV-W) (Christensen, 2016). In

particular, it is suggested that EBV activates HERV-W, so that MS disease will be developed indirectly (Fernández- Menéndez *et al.*, 2016).

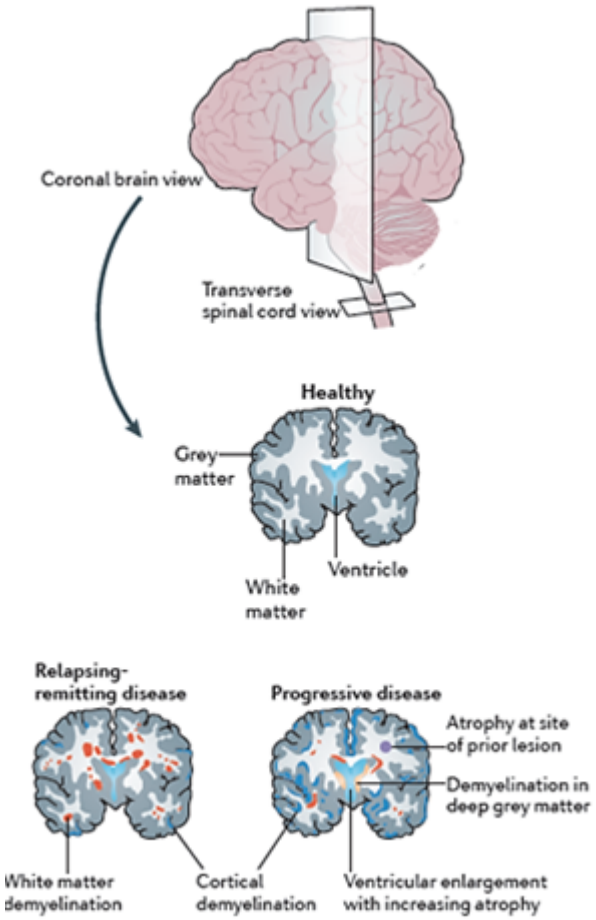


Figure 1. **The pathology of multiple sclerosis.**
The coronal brain view of the brain of a healthy individual compared to the ones of multiple sclerosis patients. Demyelinating lesions of the white and grey matter are observed in relapsing-remitting and progressive MS (adapted from Dendrou *et al.*, 2015).

## HIV characteristics

### Virology and characteristics of HIV

Human Immunodeficiency Virus (HIV) is generally transmitted through anal and vaginal sex. In addition to this, sharing drugs with HIV positive individuals through needles and

syringes is a common method of HIV transmission. Less commonly, HIV infected mothers can transmit the virus to their infants. Very rarely, HIV can be transmitted by oral sex and direct contact with wounded skin or body fluids contaminated with blood of HIV individuals (Centers for Disease Control and Prevention, 2016).

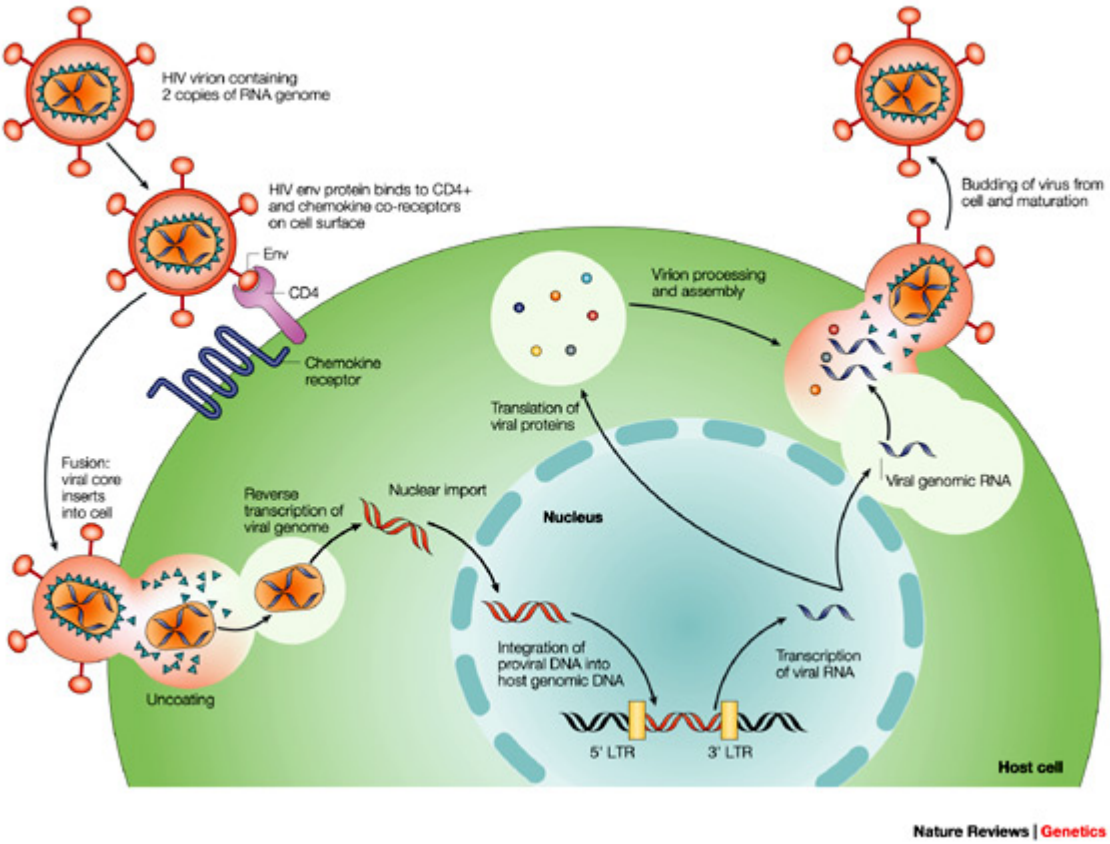


Figure 2. **HIV life cycle.** HIV binds to receptors and co-receptors of the host cell. The virus inserts cell (fusion) where it is uncoated in order the RNA genome to be reverse transcribed in the cytoplasm. DNA moves to the nucleus where it integrates into the host genomic DNA. The new viral RNA is transcribed in the nucleus or it is translated into proteins in the cytoplasm. Packaged virus particles can eventually bud from the cell (Adapted from Rambaut *et al.*, 2004).

From a virological point of view, HIV is an RNA exogenous Retrovirus. Morphologically, it is a circular virus with an estimated diameter 80-100 nm, with a conical capsid and a characteristic envelope. The virus requires a host to be entered in order to replicate itself, in a process characterised by multiple steps, which are described as follows

(Freed, 1998). Firstly, the virus is fused and uncoated so that the RNA genome is reverse transcribed (retro) into DNA in the cytoplasm. Then, DNA migrates to the nucleus where it can be integrated into the host genome. At this point, the new viral RNA may be transcribed and can be translated into proteins, which can be packaged into particles. These particles can finally bud (exit) from the cell (Figure 2). Gp120 is the HIV protein that binds to the $CD4^+$ receptor of the T-helper cells of the host's immune system (Kuritzkes *et al.*, 2008). To put it simply, receptors bind to proteins very specifically. When picturing this, we can consider electronic devices: UK plugs cannot be used in European-style plug sockets. HIV has a similar behaviour: there are two different strains of HIV binding to T-helper ($CD4^+$) cells (Figure 3). Accordingly, if HIV has the X4 strain, it binds to CXCR4 co-receptor of the targeted T-helper cell, whereas if HIV has the R5 strain, it binds to the CCR5 co-receptor of the T-helper cell (Kuritzkes *et al.*, 2008). These differences are important for treatment options, as we will discover later.

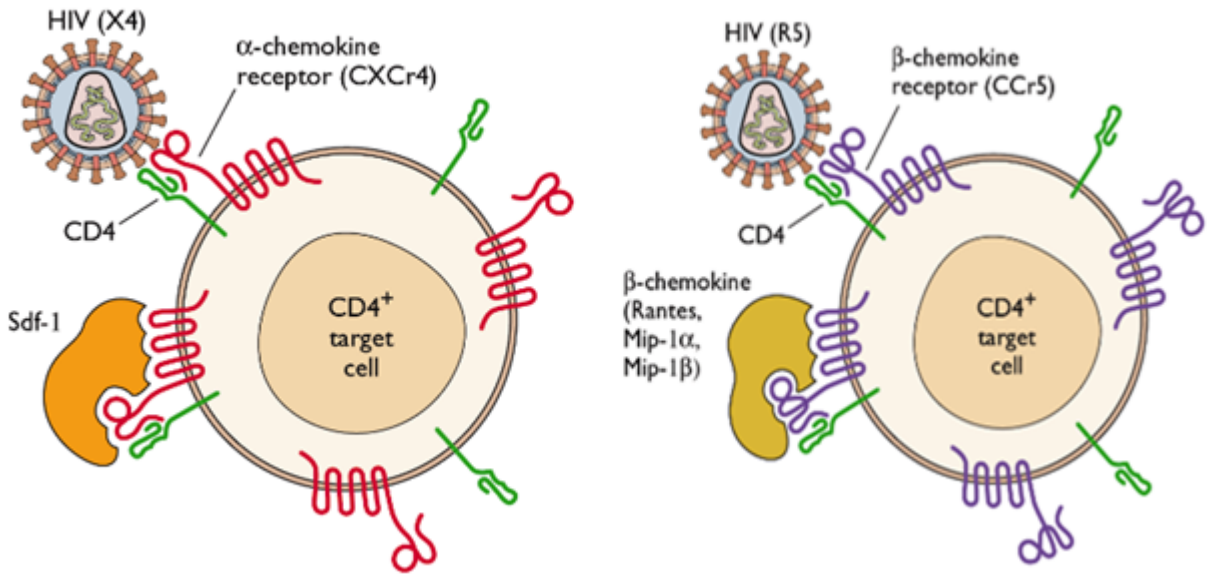


Figure 3. **The two different strains of HIV binding to T-helper ($CD4^+$) cells.** HIV X4 strain binds to T-helper cells carrying the CXCR4 co-receptors. HIV R5 strains bind to the CCR5 co-receptors of T-helper cells (Adapted from Flint *et al.*, 2009).

AIDS

One of the sexually transmitted diseases so familiar to the public is AIDS. HIV can lead to AIDS, which stands for Acquired Immuno-Deficiency Syndrome (Grill and Price, 2014). AIDS was first reported in 1981 and since then several million have been infected worldwide, making it a world epidemic (Pommier *et al.*, 2005). Progression to immunodeficiency means that our body becomes defenceless in a way that, due to gradual depletion of T-helper cells, can no longer fight pathogens on our behalf. The first nine weeks after infection, the virus can be replicated rapidly. HIV infection can be asymptomatic for up to ten years (clinical latency), so the virus needs to attack cells where it can remain for a long time, in order to achieve latency. Thus, the most common candidates of HIV latently infected cells are long-lived T-cells. These preferred T-cells must have sufficient levels of the $CD4^+$ receptor and the CCR5 co-receptor, such as the central memory T-helper cells (Churchill *et al.*, 2016).

The chronic (from Greek *chrónios*, χρόνιος, of long duration) battle between the immune system and the virus can lead to a complete lack of defence; in this way, the virus starts winning the battle, where the onset of symptoms occurs. Under these circumstances, HIV can cause chronic persistent infections and be involved in a variety of neurologic diseases (Grill and Price, 2014). Since the number of HIV copies gets increased, whereas the T-helper cells continue being decreased dramatically, patients' immune system cannot fight any kind of opportunistic infection, leading eventually to their death.

How is HIV treated?

There are no vaccines against HIV infection at the moment. Although it is extremely difficult to develop new vaccines, there are some trials that are partially successful.

Suggested treatments of AIDS have as a goal the increase of T-helper cells of the immune system, while decreasing the levels of cells infected with HIV (Delgado *et al.*, 2014). There are different classes of licensed drugs that can fight HIV, by targeting enzymes that play a key role in the HIV life cycle (Figure 2). These licensed HIV antivirals include:

a) fusion inhibitory peptides, preventing the virus from entering the cell;
b) reverse transcriptase inhibitors, interrupting reverse transcription of the virus RNA;
c) protease inhibitors, blocking the formation of the virus particles;
d) small molecule chemokine receptor antagonists (such as Maraviroc), not allowing the binding between the virus and the host cell;
e) integrase inhibitors (such as Raltegravir), hindering the virus DNA from attaching to the host genome (Figure 4).

AIDS treatment is known as Highly Active AntiRetroviral Therapy (HAART) and is a selective combination therapy of some of the HIV antiviral drug categories mentioned previously. HAART is the current most effective HIV infection therapy; it is so effective that no more new cells can be infected with HIV, making AIDS a controllable chronic disease (Lv *et al.*, 2015; Churchill *et al.*, 2016).

In 2007, Maraviroc was the first small molecule chemokine receptor antagonist that received a licence from the FDA (United States Food and Drug Administration) to be used as part of HAART combination therapy, in order to treat HIV patients (Kuritzkes *et al.*, 2008). Nevertheless, Maraviroc cannot be used in every HIV patient. Indeed, approximately half of HIV patients are not candidates for combination treatment with Maraviroc, because they are infected with the X4 HIV strain (Figure 3). In other words, Maraviroc is only effective in candidates who have been infected with HIV which binds to the CCR5 T-helper cell co-receptor (Kuritzkes *et al.*, 2008). It is very important to highlight the fact that there are two types of HIV strains, because the X4 strain (binding to CXCR4 co-receptor) is targeted with Maraviroc; instead, the cases infected with the HIV R5 strains (binding to CCR5 co-receptor), need to be targeted with a combination therapy (HAART) of some of the rest four types of enzyme inhibitors. However, there is a case of an individual infected with the R5 strain of HIV who was cured without HAART, as is described below.

The Berlin patient

There is only one person in the world who has been entirely cured from HIV infection. Indeed, this case is so unique that he has been notoriously known as 'The Berlin patient'. In 1995, Timothy Ray Brown was diagnosed as HIV positive (Huffington Post, 2015) and he was administered with the HIV treatment of that era, AZT medication. AZT was known to have severe side effects, while at that time the life expectancy of an HIV patient was rather limited. Luckily for Brown, 1995 saw HAART treatment being initiated, resulting in a rapid extension of HIV patients' life expectancy. Therefore, the Berlin patient started antiretroviral therapy that stabilized him for 11 years. However, in 2006 Brown was diagnosed with acute myeloid Leukemia. The clinician team that took over his case - based in Berlin (hence, the Berlin patient) - and suggested he receive an allogeneic bone marrow (haematopoietic stem cell) transplantation. The Berlin team identified and matched the patient to an HIV resistant donor, who had a unique genetic mutation, which made his T-helper cells lack the CCR5 co-receptor that binds to HIV (Deeks *et al.*, 2012). Currently, Timothy Brown is HIV negative.

Even if stem cell transplantation seems to be the most plausible strategy to treat HIV positive patients, such a strategy cannot be applied to an epidemic level (Churchill *et al.*, 2016). In other words, performing stem cell transplantations with bone marrow resistant to one of the two HIV strains allows us to treat patients. Yet, something like that is not feasible, given the fact that there are so many millions of HIV positive people in the world that would require transplantations.

**How MS is related to HIV**

In order to understand whether MS is related to HIV, it is worth noting that co-occurrence of MS with HIV infection itself is an unusual phenomenon, at least in scientific literature (Delgado *et al.*, 2014). For instance, a case report of 2011 described a MS patient diagnosed with HIV co-infection whose MS symptoms resolved completely after starting HIV treatment (Christensen, 2016). Therefore a case similar to that of Shana Pezaro had already been reported in 2011.

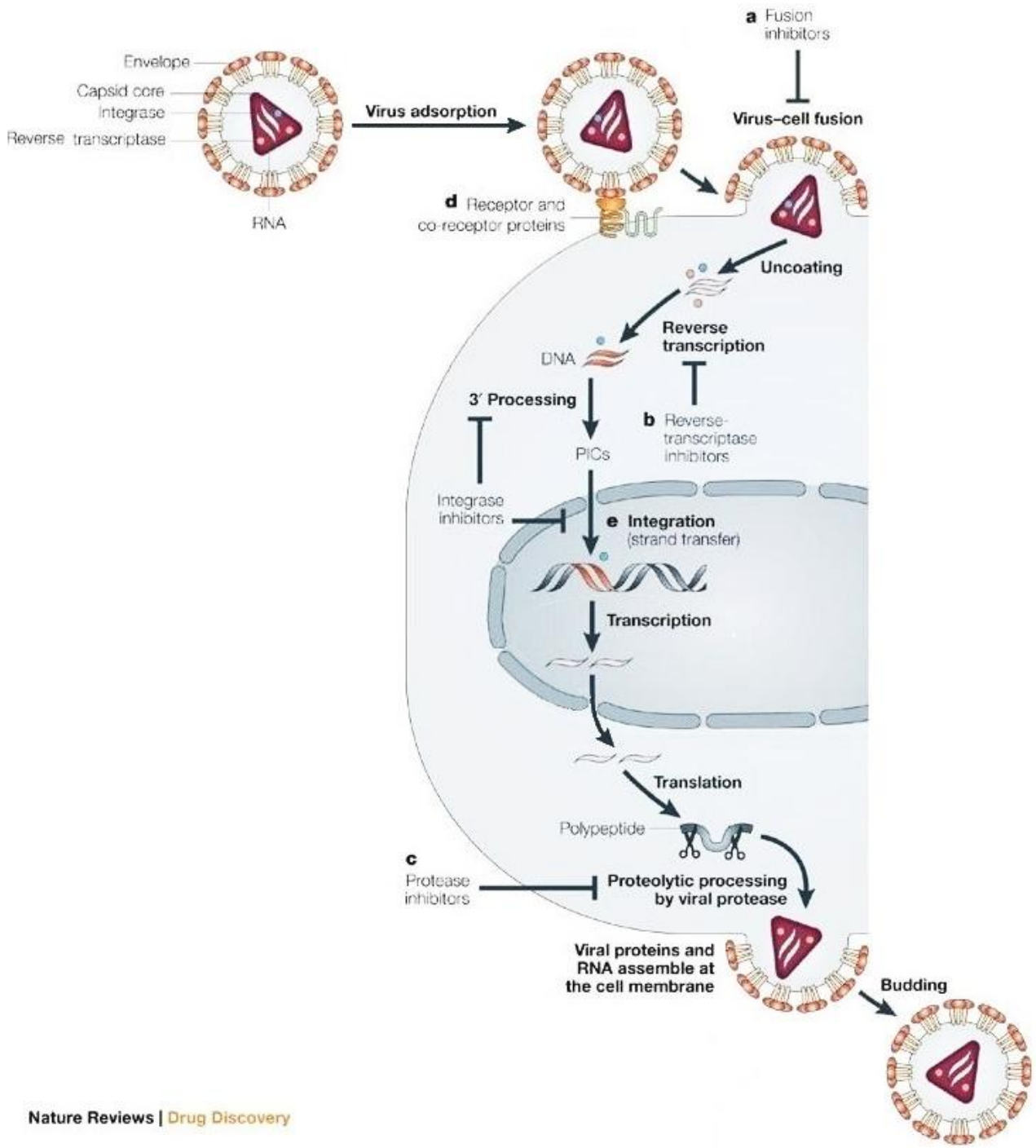


Figure 4. **HIV antivirals targeting enzymes related to the HIV replication life cycle.**

HIV antivirals target the enzymes associated with the HIV life cycle: virus fusion (a), reverse transcription (b), integration of HIV reversed transcribed genome into the host DNA to complete transcription (e) and proteolytic viral processing after translation (c). Antivirals also attack receptor and co-receptor proteins that bind to HIV strains (d) (adapted from Pommier *et al.*, 2005).

At this point, there are two theories explaining how patients with MS and HIV coinfection were temporarily or permanently free of MS symptoms. The first states that HIV immunodeficiency itself (even in the absence of antiretroviral treatment (HAART)) implies that HIV positive patients may be associated with a sort of significantly lower risk of developing MS. On the other hand, the second hypothesis, more likely than the previous one, states that the HIV therapy treats or prevents MS development (Van der Kop, 2015; Gold *et al.*, 2014).

As far as the first hypothesis is concerned, it is surprising how few cases of both MS and HIV infected patients are reported (González- Duarte *et al.*, 2011). Christensen (2016) pointed out that HIV encodes HERV-W genes that provoke HERV cell death. Meanwhile though, pharmaceutical companies neither have guidelines on how to treat HIV infected patients with MS, nor ever recall receiving such an inquiry (Gold *et al.*, 2014).

As for the second hypothesis, there are two pathways of how HIV antiretroviral drugs can treat MS: firstly in a direct way, by treating their initial target (HIV infection), which leads to suppression of potential HERV infection; or indirectly, treating HHV-6 and EBV (Herpesviruses), which activate and interact with HERVs. Either way, HIV antiretrovirals accidentally ameliorate HERVs, a responsible factor of developing MS (Weiss, 2016; Kakalacheva *et al.*, 2011; Dreyfus, 2011). If this hypothesis is proven to be correct, perhaps the few cases of MS patients with HIV co-infection could be treated with stem cell transplantation, the same strategy used to treat HIV infection of the Berlin patient.

**Can MS patients without HIV infection be treated?**

A clinical trial

Regardless of the mechanisms of how MS and HIV are related, it is of primary importance to test whether this antiretroviral therapy can treat MS patients who do not have HIV infection. A clinical trial was set in the UK to test this likelihood. This ongoing trial is called INSPIRE, which studies the efficacy of a drug, Raltegravir, in progression of disease in MS patients not infected with HIV (Giovannoni, 2013). Currently, INSPIRE is at Phase II

(Christensen, 2016) and only after the completion of Phase III the results of the use of Raltegravir can be published.

Why Raltegravir

As has already been mentioned, HAART is a combination therapy of HIV enzyme inhibitors. Raltegravir is an integrase inhibitor that blocks HIV retroviral replication. In 2007, Raltegravir became the first integrase inhibitor drug used in HAART (Deeks *et al.*, 2008). In spite of this, Raltegravir can be used as a monotherapy, as well. It contributes to the decrease of HIV infected cells while boosting patients' ability to 'defend themselves', by increasing the number of T helper cells of their immune system (Delgado *et al.*, 2014). It is suggested that Raltegravir can be effective against both retroviruses (HIV, HERVs) and DNA-viruses (HHV-6 and EBV Herpesviruses) (Dreyfus, 2011). If this is case, Raltegravir will possibly justify whether the second hypothesis is correct, whilst explaining how MS patients with HIV co-infection, like Shana Pezaro, observed treatment of their MS symptoms.

Limitations

Even though there is profound evidence that we are close to the treatment of Multiple Sclerosis, MS patients cannot gain access to this treatment unless they are HIV positive. What is more, it is unclear which of the two scenarios explains the treatment of MS symptoms, as in the case of Shana Pezaro. The difficulty of this lies in the lack of reasonable documentation of MS incidence of the pre-HAART era, covering the period between 1981 and 1995. HIV was first described in 1985, whereas HAART was first introduced only in 1995 (Gold *et al.*, 2014). The problems continue even after 1995, where it is uncertain which HIV-positive population received HAART and, if so, the duration of their exposure to it (van der Kop, 2015). In this way, random coincidence cannot be ruled out, yet, as an explanation of very few reported cases of MS and AIDS at the same time (González-Duarte *et al.*, 2011).

Nonetheless, if we attempt to cross out random coincidence, we have to think of other scenarios, such as why only a few cases resemble the one of Shana Pezaro. One of them suggests that there is a possibility of wrong diagnosis in the pre-HAART era. In particular, HIV infection in the central nervous system can be responsible for an MS-like disorder (González-Duarte *et al.*, 2011; Gold *et al.*, 2014), characterized by T-helper cell depletion (Delgado *et al.*, 2014). Another disadvantage of the pre-HAART era is the lack of neuroimaging techniques through magnetic resonance imaging (MRI) machines (Grill and Price, 2014), contributing to the misdiagnosis theory. In other words, without MRI screening available, HIV positive patients with MS-like symptoms would be diagnosed with neurological condition caused by HIV, rather than MS progression (Gold *et al.*, 2014).

## The future of MS treatment

### Suggestions for accelerating the process

Waiting for the results of one single clinical trial (INSPIRE) is not enough to reach the treatment of Multiple Sclerosis in the near future. Conclusions can be drawn faster when more published data is available, so that future studies will be focused on the correct material. The diagnosis of MS used to be performed exclusively by clinicians, based on the symptoms of the patients. Clinical Virology is a promising field for the future of diagnosis, due to the wide range of techniques that are required to give evidence in every individual case sample. Diagnostic Virology involves serology, as well as molecular and cellular Biology techniques. González-Duarte and colleagues (2011) suggested performing Polymerase Chain Reaction (PCR) in biopsies of patients with demyelinating brains. PCR, one of the gold standard molecular techniques of every Biology laboratory, is used to detect specific DNA sequences. More precisely, in those samples PCR can detect the presence or absence of viral genome, while it can also help classifying those patients as MS-patients or patients with MS-like disorder caused by HIV. Furthermore, the same study suggested that the number of T-helper cell count of MS or MS-like cases should be noted down, with the aim to create profile characterisations (González-Duarte *et al.*, 2011).

These suggestions, in addition to MRI screening, will contribute to the creation of correct databases of MS and/or HIV positive patients. These databases will be available for further studies, in case, for instance, INSPIRE fails to initiate Phase III trial. Ultimately, if Raltegravir trials succeed, it would be imperative to investigate whether this drug could be used to treat other autoimmune diseases, as well (namely: Rheumatoid Arthritis, Systemic Lupus Erythematosus, Hashimoto's Thyroid Disease) (Dreyfus, 2011). The only thing that is guaranteed at the moment is that there must be a scientific explanation of how Shana Pezaro walked after HIV antiretroviral therapy, other than pure coincidence.

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