

# Multiple Sclerosis and Subsequent Human Immunodeficiency Virus Infection: A Case with the Rare Comorbidity, Focus on Novel Treatment Issues and Review of the Literature

CHARALAMPOS SKARLIS<sup>1</sup>, MARIA GONTIKA<sup>1</sup>, SERAFEIM KATSAVOS<sup>1</sup>,  
GIORGIOS VELONAKIS<sup>2</sup>, PANAGIOTIS TOULAS<sup>2</sup> and MARIA ANAGNOSTOULI<sup>1,3</sup>

<sup>1</sup>*Immunogenetics Laboratory, 1st Department of Neurology,  
Medical School of National and Kapodistrian University of Athens, Aeginition Hospital, Athens, Greece;*  
<sup>2</sup>*Research Unit of Radiology and Medical Imaging, 2nd Department of Radiology,  
Medical School of National and Kapodistrian University of Athens, Eugenidion Hospital, Athens, Greece;*  
<sup>3</sup>*Outpatient Section of Demyelinating Diseases Clinic, 1st Department of Neurology,  
Medical School of National and Kapodistrian University of Athens, Aeginition Hospital, Athens, Greece*

**Abstract.** *Background: The comorbidity between Multiple Sclerosis (MS) and Human Immunodeficiency Virus (HIV) infection is particularly rare. Only a few cases of comorbidity of Clinically Definite (CD)-MS and HIV have been documented worldwide, while the potential beneficial role of antiretroviral therapy regarding MS activity has long been an area of debate. Case Report: We present a 36-year old male, bearing a diagnosis of CD-MS for twelve years. He had been treated for ten years with interferon-beta-1b, when he voluntarily discontinued therapy, claiming clinical stability. One year later he was diagnosed positive for HIV and he started and continued only on efavirenz/emtricitabine/tenofovir-disoproxil fumarate (ATRIPLA<sup>®</sup>), remaining relapse-free until today. Conclusion: This fact, in combination with the unique pharmaceutical composition of the drug, which contains a component similar to a newly-approved agent for MS, dimethyl fumarate, prompted us to review the literature regarding this rare comorbidity and to suggest that the role of the antiretroviral therapy should be further explored in MS.*

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system (CNS), resulting in demyelination and subsequent degeneration of the axons, affecting mainly the white, but also the gray matter (1). The neurologic complications of Human Immunodeficiency Virus (HIV) have been reported since 1982 and it has been proven that CNS constitutes a major target of the HIV (2-4). In particular, neuroinflammation and demyelination have been suggested as mechanisms causing both HIV-1-associated neurocognitive disorder (HAND) and HIV encephalopathy (HIVE) (5, 6).

The coexistence of demyelinating neurological disorders and HIV is particularly rare, especially regarding MS. Here we report the case of a patient bearing a diagnosis of clinically definite-MS (CDMS) for twelve years, who was recently diagnosed positive for HIV infection. He was started on efavirenz/emtricitabine/tenofovir disoproxil fumarate (ATRIPLA<sup>®</sup>) and remained relapse-free, without receiving any pharmacological therapy for MS. To our knowledge, this is the first case of MS-HIV comorbidity treated with this novel antiretroviral compound.

## Case Report

This is a 36-year-old white male and a known case of multiple sclerosis diagnosed 12 years ago, at the age of 24 years old. At that time, in 2003, he experienced two distinct neurological clinical attacks during a four-month period. The first attack consisted of numbness of the lower extremities with a hypoesthesia at thoracic level 3 (T3) and he was evaluated at a province hospital (PH). He did not receive any treatment and the symptoms partially resolved, regarding patient's statement, because we had not examined him that

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*Correspondence to:* Ass. Prof. Maria C. Anagnostouli, Demyelinating Diseases Clinic & Director of Immunogenetics Laboratory, 1st Department of Neurology, Medical School, National and Kapodistrian University of Athens, Aeginition Hospital, 72-74 Vassilisis Sofias Ave, 11528, Athens, Greece. Tel: +30 2107289278, Fax: +30 2107216474, e-mail: managnost@med.uoa.gr

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time. Four months later, he was hospitalized at the same PH, because of an episode of acute right optic neuritis. His rest neurological examination is referred as normal. He was treated with 1 gr intravenous (IV) methylprednisolone for five days, followed by *per os* tapering, until total remission. At that time, the performed brain magnetic resonance imaging (MRI) revealed multifocal white matter T2 lesions, without gadolinium enhancement in T1 sequences, fulfilling the McDonald and Barkhof criteria, for Multiple Sclerosis (MS) (7). He refused lumbar puncture; therefore, the oligoclonal band status is still unknown.

The patient visited for the first time the Outpatient Department of our Clinic (OTC) a few months later, in 2004. His personal history was significant for chicken pox at the age of 16 years and childhood asthma. His family history was positive for autoimmune diseases, as his mother bore a diagnosis of Hashimoto's disease. His neurological examination revealed only indifferent bilateral plantar reflexes. He had a full laboratory screening with no pathological results except for high levels of IgG immunoglobulin. He repeated brain MRI, which showed a new gadolinium enhanced parietal lesion, thus he initiated treatment with interferon beta-1b three times weekly, with satisfying responsiveness and tolerance.

During the following decade, he experienced two further clinical attacks, with an interval of two years. The first episode, in 2007, consisted of numbness of the upper extremities, with a hypoesthesia level at cervical level 5 (C5), fully remitted after three days of 1 gr IV methylprednisolone followed by *per os* tapering, at the PH. The second one, in 2009, consisted of left horizontal diplopia, partially improved after *per os* methylprednisolone treatment. During the second episode, his neurological examination revealed left horizontal diplopia and indifferent bilateral plantar reflex and his Expanded Disability Status Scale (EDSS) score was estimated at 2.00. The new MRI scanning showed non-active multifocal white matter lesions in both the brain and cervical spine, with one new periventricular lesion. In 2012, he voluntarily discontinued therapy, claiming of no symptoms and clinical stability. Until then, his Annualised Relapse Rate (ARR) was 0.44, his EDSS progression 0.22 and he had received three courses of cortisone, either intravenously or *per os*.

In 2014, he was hospitalized in the PH for a mild brain injury, after a conflict episode on the road. During his hospital evaluation, his initial blood tests showed white blood cell (WBC) 6.85 K/ $\mu$ l, lymphocytes (1.69 K/ $\mu$ l) and low platelets (60 K/ $\mu$ l) and subsequently, he was found positive for HIV. He initiated antiretroviral treatment with efavirenz (600 mg)/emtricitabine (300 mg)/tenofovir-disoproxil fumarate (200 mg) (ATRIPLA<sup>®</sup>), one tablet once a day, with satisfying responsiveness. Regarding his MS course, he remained both clinically and neuro-radiologically stable. After eight months on ATRIPLA<sup>®</sup>, his WBC were 7.5 K/ $\mu$ l and his lymphocyte

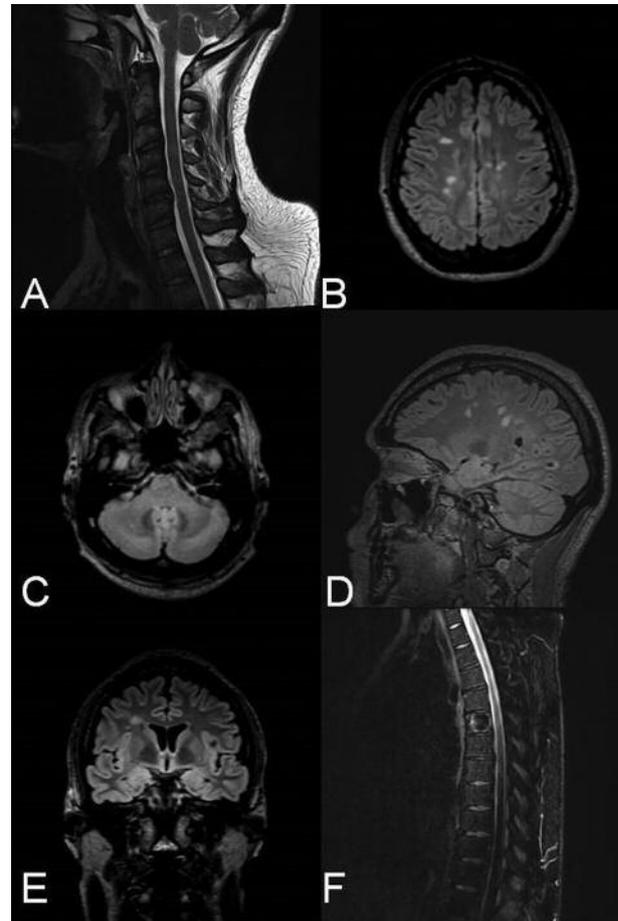


Figure 1. Patient's MRI scans after eight months on ATRIPLA. A. Cervical MRI; Sagittal T2-weighted image reveals hypertensive lesions (C2-C3, C4, C5-C6). B-C. Axial FLAIR (Fluid-attenuated inversion recovery) brain images, with characteristic chronic periventricular and juxtacortical lesions (B), and a cerebellum lesion (C). D. Sagittal FLAIR brain image with hypertensive lesions involving the corpus callosum (Dawson fingers). E. Coronal FLAIR image with right juxtacortical hypertensive lesion. F. Sagittal T2-weighted thoracic MRI, with no apparent intramedullary demyelinating lesions, T5 spinal hemangioma.

number was 1.90 K/ $\mu$ l and platelets 153 K/ $\mu$ l. His neuro-radiological scans were absolutely the same, as well (Figure 1). Today, after almost three years on this antiretroviral therapy, his ARR is 0.28, his EDSS progression 0.14, he demonstrates unidentifiable HIV blood-load, and he is fully functional, concerning activities of daily living (Table I).

## Literature Review

The coexistence of demyelinating neurological disorders and HIV is particularly rare, especially regarding MS. In 1989,

Table I. Milestones of patient's clinical course and therapy.

	2003	2004	2006	2007	2009	2014	2015
Relapses	1. Numbness of lower extremities and trunk 2. Right optic neuritis	Clinically stable	Clinically stable	Numbness of upper extremities	Left horizontal diplopia	Clinically stable	Clinically stable
EDSS	Referred as zero	1.0	1.0	No data	2.0	2.0	2.0
Corticosteroids	5 g Methyl-prednisolone, <i>per os</i> tapering	-----	-----	3 g Methyl-prednisolone, <i>per os</i> tapering	<i>Per os</i> methyl-prednisolone	-----	-----
Brain MRI	Multiple subcortical and periventricular lesions of both cerebral hemispheres	One new active left parietal lesion Gadolinium (+)	Multiple lesions of the cerebral hemispheres, one new lesion of the corpus callosum	-----	One new periventricular lesion Gadolinium (-)	-----	T2 sequences stable T1 sequences with some black holes
Cervical MRI	-----	-----	Three-Four intramedullary lesions, mainly at C2-C3 and C4 levels. Gadolinium (-)	-----	Stable	Stable	Stable
Thoracic MRI	-----	-----	-----	-----	-----	-----	Negative
DMT	-----	Interferon-b-beta	Interferon-b-beta	Interferon-b-beta	Interferon-b-beta	Discontinuation	-----
HAART	-----	-----	-----	-----	-----	ATRIPLA®	ATRIPLA®

DMT, Disease modifying therapy; HAART, high active antiretroviral therapy; EDSS, expanded disability status scale; MRI, magnetic resonance imaging; Gd, gadolinium.

Berger and collaborators were the first to describe a series of seven patients with an MS-like disease and HIV comorbidity (8, 9). Taking into consideration the primitive criteria of MS in 1989, we cannot be sure that these patients were suffering from MS *per se*, or another demyelinating disease. However, six definitive MS-HIV comorbidity cases, according to original and revised McDonald criteria, are presented in the international literature (10-15). In two reports, HIV infection was diagnosed after MS, while in those described from Chin and Facchini, HIV infection clearly preceded MS and only one the diagnosis was concomitantly (10-15). Regarding the gender of the patients, six males (including our case) and only one female are reported (Table II), in contrast to the typical finding of female prevalence in MS.

Interestingly, Maruszak *et al.* (2011) and Chalkley *et al.* (2014) describe improvement of neurological symptoms and no relapses in patients with MS and HIV infection, after receiving antiretroviral therapy (11, 12). The most striking element is that these patients showed no complications and disease progression for a long time, remaining clinically stable, similarly to the clinical status of our patient for the last two years. In 2015 Gold *et al.*, in the largest linkage study undertaken to investigate a possible association between HIV

and MS, revealed that HIV infection is associated with significantly decreased risk of developing MS (16).

## Discussion

Our patient is the first clinical case in the literature, whose MS diagnosis significantly precedes HIV infection with such a big interval. Although his total clinical course cannot be officially considered as a benign type of MS, his disease course is significant for very few relapses and minimal accumulative disability. The accidental result of HIV seropositivity, as well as the persistent stable clinical presentation while on monotherapy with highly active antiretroviral therapy (HAART), led us to investigate whether his clinical stability is associated with either the HIV infection *per se*, or with the possible effects of the HAART in MS. It is well known that concurrence of MS and HIV infection is uncommon and only six cases (fulfilling the McDonald criteria) have been reported, as presented in Table II.

Our case is the first of an MS patient with a following HIV infection treated with the novel antiretroviral drug ATRIPLA®. While on ATRIPLA® treatment, he remains relapse free, neurologically stable, and with undetectable viral load.

Table II. *Published reports of HIV and MS coexistence, type of MS, and Medications.*

Case	Gender	Age of multiple sclerosis onset	Type of multiple sclerosis	Medication for HIV	Medication for multiple sclerosis
Our Case	Male	24	Relapsing-Remitting	Efavirenz/Emtricitabine/Tenofovir disoproxil fumarate	Interferon-β
Chin <i>et al.</i> 2015	Female	34	Relapsing-Remitting	No information available	No information available
Chalkley <i>et al.</i> 2014	Male	32	Multiple Sclerosis-like	Emtricitabine/Tenofovir Nelfinavir	No information available
H.Maruszak <i>et al.</i> 2011	Male	26	Relapsing-Remitting	Nevirapine Stavudine Didanosine Abacavir Lamivudine Ritonavir Indinavir	Corticosteroids Interferon-β
Sardar <i>et al.</i> 2011	Male	35	Progressive	No information available	Solumedrol Oral steroids
Duran <i>et al.</i> 2004	Male	32	No information available	Atazanavir/Ritonavir boosted Lopinavir/Ritonavir boosted	No information available
Facchini <i>et al.</i> 2002	Male	8	No information available	No information available	Methylprednisolone Prednisolone

MS, Multiple sclerosis; HIV, human immunodeficiency virus; R-R, relapsing-remitting.

It is known, that the mechanism of action of efavirenz is through non-competitive inhibition of the HIV reverse transcriptase (17). Moreover, the mechanism of action of both tenofovir-disoproxil-fumarate (nucleotide reverse transcriptase inhibitor) and emtricitabine (nucleoside reverse transcriptase inhibitor) is based on the intracellular conversion of these drugs to their active metabolites, which competitively inhibit the activity of HIV reverse transcriptase and consequently block viral replication (17,18). In this way, the drug restores the number of CD4<sup>+</sup> lymphocytes interfering with immunomodulation. Regarding our patient, we cannot ignore the fact that fumarate is a component of ATRIPLA<sup>®</sup> as tenofovir-disoproxil-fumarate. Chalkley and colleagues also report the same clinical effect in their clinical MS-HIV case treated with tenofovir, which contains the fumarate (11).

Fumarate was recently approved by FDA as dimethyl-fumarate for MS treatment. It exerts its immunomodulatory effect by reducing the expression of cytokines tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) in glial cells, and also by mediating a strong antioxidant effect (19-23). Although it is not available in the international literature and we cannot confirm in any way the bioequivalence of these two components, the disoproxil-fumarate might somehow act as an immunomodulatory agent, leading to clinical stability. However, this working hypothesis requires extensive research.

An MS-like illness has been previously described in association with HIV-1 infection with a clinical syndrome

indistinguishable from MS (9,10). Taking into consideration the primitive criteria of MS in 1989, we cannot be sure that these patients were suffering from MS *per se* or another demyelinating disease. Reviewing the reports which fulfill the McDonald criteria we can notice that six patients were males (including our case) and only one was female, in contrast to the typical finding of female prevalence in MS. The clinical course of the patients presented was relapsing-remitting MS, in the majority of the cases (3 cases including ours). Except for one, adult patients received antiretroviral therapy and claimed clinical stability. Interestingly, Maruszak and Chalkley described improvement of MS symptoms and no relapses in their patients after initiation on antiretroviral therapy remaining clinically stable for 12 and 8 years respectively, receiving only HAART (11, 12).

Several explanations of the patient's clinical course can be supposed. First, immunodeficiency induced by HIV itself (even in the absence of antiretroviral treatment) may prevent the deterioration of MS. In specific, HIV harms immune-cell homeostasis and targets a wide range of immune cells (CD4<sup>+</sup>, CD8<sup>+</sup>) and signaling pathways overlapping with MS pathogenesis (24-31). HIV infection selectively depletes CD4<sup>+</sup> T cells, and therefore it may be considered protective against the occurrence of MS.

Second, as it is widely accepted, a decrease in regulatory T cells (Treg) drives CNS injury in MS, which is in part mediated by autoreactive CD4<sup>+</sup> T lymphocytes, in addition to increased T-helper 17 cells (Th17) and Th1 cells (30). We

could assume that the available antiretroviral therapies may restore this balance, helping to reduce the inflammatory component.

Another explanation regarding the clinical stability of all patients reported is that antiretroviral medications used to suppress HIV replication, in theory, may suppress other viral pathogens implicated in MS, like Human Endogenous Retroviruses (HERVs) and herpes viruses (32-37).

## Conclusion

In conclusion, our case report highlights the possible pathophysiological interaction between HIV and MS and the likelihood of a positive influence of HIV on the clinical course of MS, a hypothesis that needs to be further investigated. We also suggest that the probable beneficial effects of antiretroviral drugs on the progression of MS should be further explored as they could offer an alternative, apart from conventional, immunomodulatory MS therapy.

## Conflicts of Interest

The Authors declare no conflicts of interest.

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