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Dimethyl fumarate modulation of immune and antioxidant responses: application to HIV therapy

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Abstract

The persistence of chronic immune activation and oxidative stress in human immunodeficiency virus (HIV)-infected, antiretroviral drug-treated individuals are major obstacles to fully preventing HIV disease progression. The immune modulator and antioxidant dimethyl fumarate (DMF) is effective in treating immune-mediated diseases and it also has potential applications to limiting HIV disease progression. Among the relevant effects of DMF and its active metabolite monomethyl fumarate (MMF) are induction of a Th1 → Th2 lymphocyte shift, inhibition of pro-inflammatory cytokine signaling, inhibition of NF-κB nuclear translocation, inhibition of dendritic cell maturation, suppression of lymphocyte and endothelial cell adhesion molecule expression, and induction of the Nrf2-dependent antioxidant response element (ARE) and effector genes. Associated with these effects are reduced lymphocyte and monocyte infiltration into psoriatic skin lesions in humans and immune-mediated demyelinating brain lesions in rodents, which confirms potent systemic and central nervous system (CNS) effects. In addition, DMF and MMF limit HIV infection in macrophages *in vitro*, albeit by unknown mechanisms. Finally, DMF and MMF also suppress neurotoxin production from HIV-infected macrophages, which drives CNS neurodegeneration. Thus, DMF might protect against systemic and CNS complications in HIV infection through its effective suppression of immune activation, oxidative stress, HIV replication, and macrophage-associated neuronal injury.

Keywords

monomethyl fumarate; fumaric acid esters; neuroprotection; HIV; inflammation; oxidative stress; immune activation; antioxidant response; Nrf2; NF-κB

I. INTRODUCTION

Fumaric acid was initially proposed for treatment of psoriasis by the German chemist Walter Schweckendiek in 1959.[1] However, because fumaric acid is poorly absorbed after oral intake, developing a mixture of fumaric acid esters (FAEs) to achieve higher effective bioavailability after oral dosing was necessary. In 1994, an enteric-coated preparation of FAEs containing 120 mg of dimethyl fumarate (DMF) and three salts of monoethyl fumarate (MEF) was licensed in Germany under the trade name Fumaderm® for the treatment of

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psoriasis. After positive results in psoriasis treatment trials, research into the therapeutic potential of FAEs has greatly accelerated. Most recently, a DMF-containing formulation, BG-12, showed marked efficacy in Phase III multiple sclerosis clinical trials.[2, 3] Furthermore, additional *in vitro* and *in vivo* studies over the past decade have explored the therapeutic potential of FAEs for the treatment of other inflammatory diseases. With the recent FDA approval of BG-12 (brand name Tecfidera™) on March 27th, 2013 for the treatment of multiple sclerosis, the clinical application of FAEs for treating inflammatory diseases is likely to further rapidly expand. This review will assess the understanding of the mechanisms of FAEs in modulating immune responses and antioxidant responses and their potential application for treating disorders of inflammation and associated oxidative stress. Among the potential uses of FAEs is the treatment of HIV infection and its associated complications, as inflammation and oxidative stress are central to HIV pathogenesis. Notably, as DMF and MMF have been shown to effectively suppress inflammatory responses *in vivo* in both systemic and CNS compartments, DMF formulation therapy could offer adjunctive protection against both systemic and CNS complications of HIV infection.

II. PHARMACOKINETICS

Within minutes after oral intake, DMF is rapidly hydrolyzed by esterases within the small intestine to form its biologically active metabolite, monomethyl fumarate (MMF).[4] MMF, but not DMF, can be detected in serum after oral DMF ingestion. DMF is undetectable likely due its rapid hydrolysis. MMF is further metabolized through the tricarboxylic acid cycle to form H_2O and carbon dioxide, which is excreted through respiration. There is no evidence for cytochrome P450-dependent metabolism. Small amounts of non-metabolized MMF are detectable in the urine and feces.[5] In fasting healthy individuals, the half-life of MMF was estimated to be ~56 minutes and peak serum levels (mean 6 μM, range 3–10 μM) were observed at ~178 minutes (standard deviation 39 minutes) after 120 mg of oral DMF (and 95 mg of MEF).[5] When these healthy individuals ingested DMF with meals, the peak MMF serum levels increased by more than 25% in 57% of the patients, but they decreased by an average of 69% in the remaining subjects; this demonstrates that food intake increases variability in serum MMF concentrations. In a smaller study of psoriasis patients, the average half-life of MMF was estimated to be ~47 minutes with peak serum levels of 11.5 μM observed at ~219 minutes post-intake (two tablets of Fumaderm®, 240 mg DMF and 190 mg MEF).[6] In both of these pharmacokinetic studies, DMF was not detected in serum (<0.07 μM in healthy individuals). This suggests that MMF, but not DMF, is absorbed into the systemic circulation, and that MMF is the functional molecule *in vivo* that should be targeted for mechanistic studies *in vitro*. Nonetheless, Rostami-Yazdi et al. detected the mercapturic acid derivative of DMF in urine from individuals taking Fumaderm®, suggesting that DMF might indeed enter the circulation prior to being rapidly metabolized.[7] Thus, DMF might express some biological activity *in vivo*, however transiently, and therefore defining the mechanisms of action of FAEs requires the study of both MMF and DMF to fully define the biological effects of oral DMF formulation therapy.

III. FAE THEARAPY SAFETY AND ADVERSE EVENTS

Oral DMF (240 mg taken 2–3 times daily) has been tested in several clinical trials in individuals with psoriasis,[8, 9] multiple sclerosis,[2, 3, 10] and other inflammatory diseases.[11, 12] The recent phase III efficacy trials for multiple sclerosis demonstrated no increase rate of patient dropout in drug vs. placebo-treated patients, indicating excellent long-term tolerability.[2, 3] The most common reported adverse events in these trials were flushing in ~33% of patients, gastrointestinal events (diarrhea, nausea, upper abdominal pain, and vomiting) in ~33% of patients, and pruritus and proteinuria in ~9% of patients. Flushing and gastrointestinal events decreased after the first month of therapy. Transient eosinophilia has

also been reported in patients at 4–8 weeks post initiation of FAE therapy.[13] DMF formulation treatment was associated with a persistent leukocytopenia (~11% reduction in white blood cell count) and particularly lymphocytopenia (~30% reduction in circulating T-lymphocytes). White-cell and lymphocyte counts decreased in patients over the first year of DMF therapy and eventually plateaued at a lower set-point, though the majority of patients' cell counts remained within the normal range. White-cell counts less than 3.0×10^9 per liter and lymphocyte counts of less that 0.5×10^9 per liter (corresponding to the National Cancer Institute Common Toxicity Criteria grade 2 or higher leukocytopenia and grade 3 or higher lymphocytopenia, respectively) were seen in ~4–7% of patients in the oral DMF groups versus ~1% in patients in the placebo group.[2, 3]

Despite the reduced white blood cell and lymphocyte counts, an increase in risk for malignancy or infection, including opportunistic infections, has not been reported in any FAE clinical trials or retrospective studies during the 20 years of FAE use.[8, 14] However, recent case reports of progressive multifocal leukoencephalopathy (PML) have been reported in patients taking combination formulations of DMF and other fumarate derivatives (Fumaderm® and Psorinovo).[15–17] Significant confounding risk factors for PML were present in these patients (including sarcoidosis, cancer, and efalizumab use) and so the true relative risk, if any, for FAE-associated PML is difficult to assess. Notably, to date, there is no evidence that patients treated with oral DMF monotherapy (BG-12/Tecfidera™) are at increased risk for opportunistic infections, including PML.[17] Nonetheless, the rare case reports of PML (180,000 patents-years of experience with Fumdaerm®), suggest that vigilance in prescribers is critical. Prior to these reports, precautions for use such as monitoring blood lymphocyte levels had been suggested. A reduction of FAE dose or discontinuation was recommended if the white blood cell or lymphocyte counts fall below 3.0×10^9 or 0.5×10^9 cells per liter, respectively.[18] This recommendation is especially prudent, in view of these recent PML case reports.

IV. MODE OF ACTION IN DIFFERENT CELL LINEAGES: IMMUNOMODULATION AND ANTIOXIDANT RESPONSE

The effects of DMF and MMF on immune responses have thus far been only partially characterized. Several *in vitro* studies have demonstrated perturbation of nuclear factor κB (NF-κB) function through inhibition of NF-κB nuclear translocation and DNA binding (Figure 1). The NF-κB pathway plays a central role in regulating cytokine production, cellular activation, development, survival, and the innate and adaptive immune system among other roles (reviewed in[19]). NF-κB has been shown to induce TNFα, iNOS, IL-1, IL-2, IL-6, ICAM-1, and COX-2, among others.[20] DMF and MMF also induce the nuclear factor erythroid-2 related factor-2 (Nrf2)-dependent antioxidant response element (ARE) pathway (Figure 1). The ARE response is a ubiquitous cytoprotective cellular stress response involving induction of multiple genes that protect cells from many forms of intracellular oxidative stress and injury (reviewed in[21]). Generally, oxidative stress occurs when cells are unable to detoxify injurious agents or repair damage resulting from reactive oxygen species, hydrogen peroxide, hydroxyl radicals, and other mediators of oxidative stress. Oxidative stress induces the translocation of Nrf2 to the nucleus where it binds to the ARE promoter element and activates gene transcription[22–24] of hundreds of genes,[23, 25, 26] including many antioxidant defense enzymes such as the sentinel cytoprotectant heme oxygenase-1 (HO-1),[27] NAD(P)H quinone oxidoreductase-1 (NQO1),[28] γ-glutamate cysteine ligase catalytic subunit (GCLC),[29] glutathione S-transferase (GST),[30] and the cysteine/glutamate transporter (xCT).[31]

Many studies have demonstrated complex regulatory interactions between the FAE-responsive Nrf2-dependent ARE and NF-κB pathways. ARE induction can inhibit the NF-

κB pathway and thus indirectly modulate inflammatory cytokine and chemokine signaling.[32] This inhibition of NF-κB likely occurs through ARE-driven reduction in oxidative stress, which has been shown to activate the NF-κB signaling pathway.[33–36] Further supporting a role for Nrf2, several studies have demonstrated increased NF-κB activation and dysregulation of cytokines and chemokines in $Nrf2^{-/-}$ mice after inflammatory insults such as exposure to lipopolysaccharide (LPS)[37] or TNFα,[37] after infection with respiratory syncytial virus,[38] and after traumatic brain injury.[39] Direct pharmacologic activators of Nrf2 such as tert-butylhydroquinone, sulforaphane, and phenethyl isothiocyanate also attenuate NF-κB activation *in vitro*.[40–43] Complicating the Nrf2 -NF-κB regulation, a reciprocal effect of NF-κB on Nrf2 function has been demonstrated.[44] The NF-κB p65 subunit has been shown to repress Nrf2 signaling at the transcriptional level, through competition with Nrf2 for transcription co-activator CREB binding protein (CBP) and through recruitment of histone deacetylase 3, resulting in local hypoacetylation of the ARE promoter element and the consequent suppression of Nrf2 signaling.[44] Thus, the Nrf2 and NF-κB pathways regulate each other through reciprocal inhibition (Figure 1). Additional studies are needed to further define the complex interactions between the NF-κB and Nrf2 pathways believed to be responsible for the effects of DMF and MMF. Through a combination of ARE induction and NF-κB signaling inhibition (Figure 1), and as yet undefined effects of other pathways, FAEs can promote an anti-inflammatory, anti-infiltrative, and anti-oxidative cellular state in multiple cell lineages, particularly immune cells. Notably, T-lymphocytes and cells of the monocyte lineage appear to be particularly sensitive to FAE exposure. The effects of DMF and MMF exposure on individual cell lineages is described in detail below and summarized in Table 1.

A. Effect of FAE in T-lymphocytes

Early studies of Fumaderm® for psoriasis treatment demonstrated a significant decline (~30%) in lymphocytes, particularly T-lymphocytes, in 94% of treated patients.[45] Similar results were observed in recent Phase III Multiple Sclerosis trials with the DMF formulation BG-12 (240 mg of DMF 2–3 times daily).[2, 3] However, the mechanism of DMF-induced lymphocytopenia is unknown. *In vitro* studies have demonstrated that DMF, but not MMF, induces apoptosis in human T-lymphocytes after 48 hours of exposure to a concentration of ~70 μM, which is 10-fold higher than the MMF serum levels achieved with oral DMF dosing.[46] This *in vitro* apoptotic effect of DMF was not seen at ~7uM, the physiologic concentration achieved by its primary *in vivo* metabolite MMF. Because DMF is not detectable *in vivo* after oral dosing, the contribution of direct DMF cytotoxicity to this lymphocytopenia is questionable. Thus further studies of the effects of long term exposure of MMF on T-lymphocyte viability and proliferation are needed.

Analyses of the immunomodulatory effects of FAEs on human T-lymphocytes demonstrated that FAEs alter cytokine production, cytokine and chemokine receptor expression, and adhesion molecule expression. Both DMF and MMF increased the production of multiple Th2 cytokines (IL-4, IL-10)[47–49] in T-lymphocytes. Furthermore, DMF, but not MMF, suppressed Th1 cytokine (IFN-γ) release and chemokine receptor (CXCR3) expression, as well as the skin-homing chemokine receptor CCR10.[50] In contrast, DMF exposure decreased release of IL-6,[50] a cytokine that inhibits Th1 polarization and promotes Th2 differentiation. The suppression of Th1 cytokine release and chemokine receptor expression is likely linked to DMF's ability to inhibit NF-κB DNA binding in T-lymphocytes,[51] an effect that is not induced by MMF *in vitro*. In line with these findings, DMF inhibited IFN-γ- and LPS-induced Th1 chemokine (CXCL9 and CXCL10) production in a dose dependent manner in human peripheral blood mononuclear cells (PBMC).[52] Furthermore, DMF was able to increase the expression of Th2 cytokines in lymphocytes in multiple sclerosis patients and mice with herpes stromal keratitis (see section V. FAEs In Inflammatory

Diseases for further discussion), suggesting that DMF treatment maintains the Th1 to Th2 shift in the setting of superimposed infections and other inflammatory states. The persistence of this Th1 to Th2 shift after DMF therapy is stopped has not been reported.

DMF has also been shown to reduce adhesion molecule expression (CD25, HLA-DR, and cutaneous lymphocyte-associated antigen) in treated T-lymphocytes, which can explain the decreased binding of treated lymphocytes to E-selectin, P-selectin, and VCAM-1.[53] Such effects might also explain reduced leukocyte rolling and adhesion in DMF-treated mice.[53] As many of these *in vitro* effects were either not studied or were not observed with MMF treatment, it is unknown if they occur *in vivo* in DMF-treated subjects. Furthermore, the roles for DMF and MMF in Nrf2-driven ARE activation in T-lymphocytes, beyond its associated NF-κB modulation, have not been studied. Thus, although limited in scope, these *in vitro* studies suggest that DMF, and MMF in part, promote a shift from a pro-inflammatory, IFN-γ-driven Th1 T-lymphocyte profile to an anti-inflammatory, IL-10-driven Th2 T-lymphocyte profile. Such a shift from a Th1 response (autoimmune responses and the killing intracellular parasites) to a Th2 response associated with eosinophilic responses and counteraction against Th1 responses could result in decreased T-lymphocyte activation and tissue infiltration *in vivo*.

B. Effect of FAE in B-Lymphocytes

Studies of the direct effects of FAE on B-Lymphocyte function have not been reported. However, there is evidence that disruption of NF-κB signaling can interfere with B-lymphocyte development and survival,[19] suggesting FAE-mediated NF-κB modulation may alter Blymphocyte function.

C. Effect of FAE in Monocytes/Macrophages/Microglia

DMF and MMF express potent anti-inflammatory and antioxidant effects in monocytes, monocyte-derived macrophages, and microglia. In human macrophages, DMF and MMF decreased NF-κB nuclear translocation and DNA binding in response to TNFα exposure and reduced TNFα secretion in response to phytohaemagglutinin, suggesting a decreased state of activation.[54] Furthermore, DMF and MMF suppressed CCL2-induced chemotaxis of human monocytes,[54] which would likely result in decreased infiltration across endothelial surfaces into tissue. In LPS-activated microglia, DMF has been shown to decrease release of the pro-inflammatory cytokines IL-1β, IL-6, and TNFα,[55] likely through decreased NF-κB signaling. DMF- and MMF-induced expression of Nrf2-dependent ARE proteins, including the ubiquitous cytoprotectant enzyme HO-1, was also reported in macrophages and microglia,[54, 56] suggesting that FAEs can modulate the oxidative state within these cells. However, DMF- and MMF-treated monocytes expressed higher levels of reactive oxygen intermediates in the respiratory burst,[57] a rapid release of free radicals that is essential step in immunological defense, particularly against bacteria and fungi. In contrast, induction of HO-1 can also decrease expression of reactive nitrogen species, another principal component of the respiratory burst, through suppression of the inducible nitric oxide synthase (iNOS) expression and associated nitric oxide induction.[58] Overall, these data suggest that DMF and MMF have potent anti-inflammatory and anti-oxidative effects in macrophages and microglia and this further suggests that DMF formulations could be effective in treating both systemic and CNS inflammatory diseases that involve macrophage/microglial activation.

D. Effect of FAE in Dendritic Cells

Both DMF and MMF suppress monocyte-derived dendritic cell differentiation and cytokine production *in vitro* through suppression of both NF-κB and extracellular signal-regulated kinase 1 and 2 (ERK1/2) signaling.[59, 60] In addition, MMF decreased IL-12, IL-10, TNFα,

and IFN-γ secretion from dendritic cells, which resulted in decreased dendritic cell effectiveness in stimulating Th1 cytokine production in T-lymphocytes.[61, 62] DMF exposure to dendritic cells also decreased inflammatory cytokine production (IL-12, IL-23, and IL-6), dendritic cell maturation, and effectiveness in generating activated T-lymphocytes[60]. These findings, coupled with reports demonstrating that DMF exposure increases the production of IL-10 by dendritic cells, suggest that DMF promotes the type II dendritic cell phenotype.[63] In summary, FAE interference with dendritic cell differentiation and cytokine secretion further suppresses Th1 responses in addition to the direct effects of FAEs on T-lymphocytes and also promotes a type II dendritic cell response.

E. Effects of FAE in Endothelial Cells

Similar to DMF effects in T-lymphocytes, macrophages, and dendritic cells, DMF has been shown to decrease TNFα-induced NF-κB activation and associated activation of vascular endothelial cells.[64, 65] DMF also decreased the expression of the adhesion molecules E-selectin, VCAM-1, and ICAM-1 on endothelial cells, resulting in decreased leukocyte rolling, firm adhesion, and diapedesis *in vitro*,[66, 67] perhaps through inhibition of NF-κB activation. Notably, these effects were not seen with MMF, which might indicate that DMF formulations might not induce these effects after oral administration. Nonetheless, these results suggest a second mechanism (decreased adhesion and transendothelial migration) by which FAEs decrease immune cell migration into tissues, in addition to direct effects on chemotaxis by exposed lymphocytes and mononuclear phagocytes, which could further limit tissue inflammation.

F. Effects of FAE in CNS Cells

The effects of FAEs in the CNS could be expressed through modulation of macrophages, microglia, endothelial cells, astrocytes, neurons, oligodendrocytes, and choroid plexus cells. Among those cell types in which FAE effects have been examined are monocyte-derived macrophages, microglia, endothelial cells (previously discussed), astrocytes, neurons, and oligodendrocytes. No studies of DMF or MMF effects in choroid plexus-derived cells have been published. DMF has been shown to decrease IL-1β, IL-6, and TNFα release from astrocytes and microglia,[55, 68] which could contribute to an anti-inflammatory effect in the CNS compartment. Furthermore, DMF and MMF, through Nrf2 activation, induced the expression of ARE effector proteins, including NAD(P)H quinone oxidoreductase-1 and HO-1, in microglia, astrocytes, and neurons.[55, 69, 70] Such induction of antioxidant enzymes in astrocytes and neurons was shown to protect against oxidative injury and glutamate toxicity.[69–71] Despite this protection in astrocytes and neurons, DMF and MMF did not protect against oxidative injury in the oligodendrocyte CG4 cell line.[72] These studies and those mentioned above suggest a role for FAEs as both indirect neuroprotectants through anti-inflammatory and anti-oxidative effects in macrophages, microglia, astrocytes, and endothelial cells, and as direct neuroprotectants through induction of the ARE in neurons.

V. FAEs IN INFLAMMATORY DISEASES

A. Psoriasis

Psoriasis is a common (1–3% of the worldwide population), systemic T-lymphocyte-mediated chronic inflammatory skin disease characterized by cutaneous inflammation, increased epidermal proliferation, abnormal keratinization, and appearance of erythematous plaques (reviewed in[73]). Psoriasis is the disease for which FAEs have been most widely applied for therapeutic benefit. The efficacy of FAEs likely results from their potent anti-inflammatory and antioxidant effects.

1. Inflammation in Psoriasis—Early reports demonstrated persistent Th1 T-lymphocyte activation within psoriatic plaques,[74–76] although natural killer T-lymphocytes were also implicated.[77–79] Recent work has shown a significantly complicated picture of the inflammatory milieu in psoriasis plaques. Current models now incorporate an inflammatory axis that balances the Th1, Th2, Th17, and T-regulatory type responses as well as contributions by dendritic cells, natural killer T-lymphocytes, and macrophages (reviewed in[80]). Underscoring this central role of inflammation in the pathogenesis of psoriasis, numerous immunomodulatory therapies have shown efficacy in treating psoriasis, including corticosteroids,[81] tacrolimus,[82] pimecrolimus,[83] methotrexate,[84] and the TNFα inhibiting therapies etanercept,[85] infliximab,[86] and adalimumab.[87]

2. Oxidative Stress in Psoriasis—In addition to markers of immune activation, markers of oxidative stress are consistently elevated in psoriasis patients and coupled with antioxidant dysfunction. These patients have increased carbonylation (oxidative stress marker) of macromolecules in skin biopsies and cultured fibroblasts,[88] increased plasma malondialdehyde (lipid peroxidation product),[89] increased urine 8-hydroxydeoxyguanosine (a marker of DNA oxidation) and nitrate (a product of nitric oxide),[90] increased lipid hydroperoxides,[91] and lower serum antioxidants, including paraoxonase-1 and thiols.[89, 91, 92] Furthermore, the 55 L/M allele of paraoxonase-1 (an antioxidant enzyme implicated in psoriasis that hydrolyses lipid peroxidases) is a risk factor for psoriasis and allele carriers have higher levels of oxidative stress and lower ARE activity.[93] In summary, psoriasis is a chronic inflammatory skin diseases involving numerous immune axes, particularly various arms of the T-lymphocyte axis, and elevated oxidative stress and impaired antioxidant responses.

3. Clinical Trials of FAEs in Psoriasis—Before the roles for immune activation and oxidative stress in psoriasis were identified, the German chemist Walter Schweckendiek empirically developed an FAE therapy for psoriasis.[1] Although unknown at that time, the anti-inflammatory effects through suppression of NF-κB activity and oxidative stress reducing effects through induction of the ARE suggest a role for FAEs in treating psoriasis. The first randomized, double-blind trial of FAE therapy for psoriasis was published by Nugteren-Huying et al. in 1990.[94] This trial demonstrated an average reduction in the psoriatic skin lesion area by 68% in 39 psoriasis patients treated with a combination of DMF and MEF for 4 months, an effect significantly different from the groups treated with an MEF/octylhydrogen-fumarate combination or with a placebo. Since that initial trial, other larger and longer-term clinical trials (up to 3 years) have affirmed the effectiveness and safety of FAE therapy for patients with severe psoriasis.[9, 13, 95–99] Combining DMF with other FAEs including MEF (Fumaderm®) showed greater efficacy and patient adherence to FAE therapy than DMF monotherapy.[95, 97] The mechanism for this synergistic effect is unknown, but likely could be due to competitive metabolism.

4. FAE effects on keratinocytes: role in psoriasis—The mechanisms of action of FAE therapy in effectively treating psoriasis likely represent both direct effects on keratinocytes and the aforementioned immunomodulatory and anti-oxidative properties of DMF and MMF on other cell types. Keratinocytes play a major role in the inflammatory response in psoriasis through expression of chemokines and cytokines (reviewed in[100]). DMF treatment in co-cultured keratinocytes and T-lymphocytes increased the Th2 cytokine IL-10, while decreasing IFN-γ, IL-6, and TGFα.[48] Furthermore, DMF inhibited the expression of the chemokines CXCL1, CXCL8, CXCL9, CXCL10, and CXCL11 in primary human keratinocytes.[52] These immunomodulatory effects on keratinocytes have not been tested with MMF. However, DMF and to a lesser extent MMF have been shown to decrease keratinocyte proliferation.[101, 102] In clinical studies, DMF treatment of psoriasis in patients

resulted in improved epidermal hyperproliferation, epidermal thickness, and keratinocyte differentiation.[98] Overall, these direct effects on keratinocytes suggest multiple mechanisms that modulate chemoattraction of macrophages, T-lymphocytes, and neutrophilic granulocytes and pathologic proliferation of keratinocytes.

5. FAEs reduce immune cell infiltration in psoriasis and other skin disorders—Psoriasis involves infiltration of the dermis by CD4+ T-lymphocytes and the epidermis by CD8+ T-lymphocytes, the majority of which are CD45RO+ (memory effector).[103–106] Clinical studies have demonstrated that DMF treatment of psoriasis patients for sixteen weeks decreases CD3+CD4+CD45RO+ T-lymphocytes in the dermis and CD3+ CD8+ CD45RO+ T-lymphocytes in the epidermis.[98] This FAE effect of decreased immune cell infiltration is supported by the demonstrations of FAE efficacy in decreasing immune cell infiltration in other inflammatory skin diseases. These include disseminated granuloma annulare[11, 107] and recalcitrant cutaneous sarcoidosis,[12] each of which involves large number of CD3+ lymphocytes and CD3+/CD68+ mononuclear phagocytes, each of which is suspected to result from unregulated Th1 reaction. These *in vivo* findings are consistent with *in vitro* studies of DMF that demonstrate decreased expression of adhesion molecules in endothelial cells[66, 67] and lymphocytes[53] and decreased CCL2-induced chemotaxis in macrophages[54], resulting in decreased immune cell tissue infiltration into tissues. Of note, DMF also decreased T-lymphocyte expression of the chemokine CCR10,[50] which is often expressed on skin-homing T-lymphocytes. In addition to decreased chemotaxis and homing in DMF-exposed macrophage and T-lymphocytes, induction of leukocytopenia and lymphocytopenia by DMF might also contribute to DMF efficacy in treating psoriasis.[2, 3, 8–10]

B. Multiple Sclerosis

Multiple sclerosis is the most common cause of neurological disability in young adults worldwide with approximately 2.1 million cases worldwide and 400,000 cases in the United States.[108, 109] Epidemiologic data suggest that multiple sclerosis pathogenesis involves environmental influences occurring on a background of genetic susceptibility.[110] In most patients, multiple sclerosis presents as a relapsing-remitting disease characterized by dynamic inflammatory demyelinating lesions in the CNS that are associated with sensory (~30%) or motor (~13%) disturbance of the limbs, partial or complete visual loss (~16%) and other signs and symptoms (reviewed in[111]). Multiple sclerosis is the first CNS disease successfully treated with FAEs. The efficacy of FAEs in multiple sclerosis likely results from their potent anti-inflammatory and antioxidant effects within the CNS compartment.

1. Inflammation and Degeneration in Multiple Sclerosis—Traditionally multiple sclerosis was considered to be an autoimmune, inflammatory disease of the CNS mediated by an aberrant T-lymphocyte attack against CNS elements, particularly myelin, resulting in degeneration of axons.[112] This view was strongly supported by pathological, laboratory, radiological, genetic, epidemiological, and therapeutic data, all of which supported an autoimmune and inflammatory phenotype that is driven by Th1 type inflammation in the brain (reviewed in[112]). However, recently published studies have posited that multiple sclerosis is primarily a degenerative disorder, with a secondary immune response to myelin and other highly immunogenic debris (reviewed in[113]). Evidence for this includes reports demonstrating that myelin abnormalities might begin at the inner myelin sheath in areas outside focal inflammation;[114, 115] patients in early stages of multiple sclerosis show little evidence of T-lymphocyte or B-lymphocyte infiltration in newly formed demyelinating lesions (although evidence of the innate immune response by macrophage infiltration and microglial activation is present, probably for clearing debris);[116, 117] and the ineffectiveness of autologous hematopoietic stem-cell transplantation to halt the progression of

demyelination, axonal degeneration, and brain atrophy despite reducing CNS inflammatory activity.[118, 119] Regardless of the initial pathologic substrate, the inflammatory response present in relapsing-remitting multiple sclerosis plays a critical role in disease pathogenesis as evidenced by the success of numerous immune modulators, including interferon beta-1b[100] and beta-1a,[120, 121] glatiramer acetate,[122, 123] fingolimod,[81, 124] and teriflunomide[125] among many others, in reducing and in some instances eliminating neuroinflammation and clinical relapses.

2. Clinical Trials of FAEs for Multiple Sclerosis Treatment—BG-12, an oral FAE formulation containing DMF, recently showed strong positive effects in two independent placebo-controlled phase III clinical trials (DEFINE and CONFIRM) involving more than 2600 relapsing-remitting multiple sclerosis patients.[2, 3] Importantly, BG-12 improved clinical outcomes associated with suppression of brain inflammation in such patients when given twice daily or three times daily, likely due in part to the CNS penetrance of MMF.[70] BG-12 therapy in both trials significantly reduced the proportion of patients who relapsed and the annualized relapse rate at 2 years by ~50%. Furthermore, BG-12 reduced the number of gadolinium-enhancing lesions (inflammation) and of new or enlarging T2-weighted hyperintense lesions (demyelination). In the DEFINE trial,[2] BG-12 significantly reduced progression of disability by 38% with BG-12 twice daily and 34% with BG-12 thrice daily. In the CONFIRM trial,[3] BG-12 also reduced progression of disability, but the trend was not significant. Given the positive results of these clinical trials BG-12 was approved for the treatment of multiple sclerosis by the FDA on March 27th, 2013 under the brand name Tecfidera™. These results show that the oral DMF formulation (BG-12/ Tecfidera™) is effective in modifying CNS inflammation and associated neurological dysfunction in treated patients and they suggest that DMF formulations should be considered for use in other neuroinflammatory diseases.

3. FAE Immune Modulation in Multiple Sclerosis—The balance between Th2 and Th1 responses plays a key role in multiple sclerosis pathogenesis. Multiple sclerosis lesions contain activated CD4+ and CD8+ T-lymphocytes, mononuclear phagocytes, and high expression of IFN-γ, TNFα, IL-1, and leukocyte and vascular adhesion molecules.[126–128] A shift from a Th1 towards a Th2 cytokine profile, as induced by FAEs in T-lymphocytes and PBMCs *in vitro*,[47–50, 52] could have a beneficial effect on the clinical course of the disease. This is supported by a recent study that showed that BG-12-treated multiple sclerosis patients showed increased intracellular expression of the Th2 cytokine IL-10 in CD4+ peripheral lymphocytes, with no change in IFN-γ expression.[129] It has also been proposed that the mild leukocytopenia and lymphocytopenia observed in BG-12 treated individuals could contribute to BG-12 efficacy by reducing the number of circulating immune cells.[130] A possible complimentary mechanism for the efficacy of BG-12 in multiple sclerosis is the decreased expression of adhesion molecules on endothelial cells[66, 67] and lymphocytes[53] and decreased CCL2-induced chemotaxis in macrophages[54], resulting in decreased immune cell tissue infiltration into the brain. Each of these mechanisms is supported by studies of autoimmune encephalomyelitis (EAE), the murine model of multiple sclerosis. During chronic EAE, MMF significantly and DMF nonsignifcantly reduced the infiltration of T-lymphocytes in the spinal cord. Additionally, MMF, and to a lesser degree DMF, significantly reduced the infiltration of macrophages into the spinal cord.[131] Thus, although the major beneficial effects of BG-12/Tecfidera™ in treating multiple sclerosis are likely associated primarily with the ability to reduce CNS inflammation, the reduction of levels of circulating T lymphocytes and reduction of T-lymphocyte and monocyte/macrophage chemotaxis might also contribute to the beneficial effects in multiple sclerosis.

4. FAE Antioxidant Response Induction in Multiple Sclerosis—The emerging and prominent role for oxidative stress in multiple sclerosis pathogenesis and the well studied protective effects of the ARE activation in cell of different lineages in the CNS highlight another probable mechanism of FAE efficacy in multiple sclerosis. Oxidative stress associated with mitochondrial dysfunction[132] and excessive release of free radicals[133] has been strongly associated with multiple sclerosis pathogenesis, perhaps contributing to increased CNS leukocyte invasion and activation, neurodegeneration, and oligodendrocyte damage. Free radicals include reactive oxygen species, reactive nitrogen species, and nitric oxide, which are mainly produced by macrophages and microglia.[134, 135] In addition, myeloperoxidase activity, which produces the cytotoxic oxidizer hypochlorous acid and tyrosyl radicals catalyzed from H_2O_2, is elevated in macrophages and microglia in actively demyelinating white matter and cortical lesions in multiple sclerosis.[136] These data suggest that a reduction in oxidative stress might reduce neuroinflammation and associated CNS damage, each of which could be suppressed by BG-12.

BG-12 is the first multiple sclerosis therapy shown to activate the Nrf2-dependent ARE pathway and thus reduce oxidative stress. Previous studies have shown that FAE induction of the ARE and its effector proteins, including HO-1, prevented oxidative-stress induced astrocyte and neuronal injury,[69, 70, 137] decreased microglia nitric oxide burst,[72] and prevented myelin loss within the CNS.[70] In EAE studies, DMF treatment attenuated axonal loss and reduced astrocyte activation in wild-type mice, but not in $Nrf2^{-/-}$ knockout mice,[70] strongly suggesting a role for Nrf2-dependent ARE activation in FAE-mediated neuroprotection. This finding is supported by *in vitro* data that demonstrated that Nrf2 knockdown removed the dose-dependent protective effect of DMF and MMF on astrocyte and neuron cell viability after toxic oxidative challenge.[69] High concentrations (100 μM) of DMF and MMF have been shown to induce the ARE protein HO-1 in oligodendrocytes without evidence of drug cytotoxicity.[138] However, whether FAEs are directly protective against oxidative injury or other insults in oligodendrocytes has not been reported. Despite this strong evidence linking ARE induction to protection during CNS oxidative and inflammatory injury in multiple sclerosis, the specific antioxidant pathways and effector proteins responsible for these protective effects are not known.

C. Other Inflammatory Diseases as Targets for FAEs

1. Huntington's Disease—FAEs have been studied preclinically in other diseases linked to inflammation and oxidative stress. Huntington's Disease (HD) is an autosomal dominant, progressive neurodegenerative genetic disorder, associated with an expanded trinucleotide (CAG)n repeat encoding a polyglutamine stretch in the N-terminus of the huntingtin protein.[139] Oxidative stress, mitochondrial dysfunction, and other metabolic deficits have been shown to play central roles in the pathogenesis of HD.[140] Furthermore, symptomatic CNS disease staging in HD model mice was associated with increased levels of brain oxygen radicals.[141] Treatment of these HD model mice with DMF prolonged survival and preserved motor functions and neuronal morphology within the striatum and motor cortex,[6] likely through the induction of the ARE. These findings implicate a central role for oxidative stress in HD pathology and have led to multiple clinical trials studying the efficacy of various antioxidants and modulators of the Nrf-2/ARE pathway,[142] though FAEs have not yet been studied clinically in HD. The efficacy of FAEs in this model and in multiple sclerosis suggests a broader applicability to CNS disease states with oxidative stress components, regardless of cause.

2. Herpes Stromal Keratitis—Herpes Stromal Keratitis (HSK), the leading cause of infectious blindness in developed nations,[143] is a disease characterized by an immune-based pathological reaction that is triggered by herpes simplex virus (HSV) infection of the cornea.

In HSK, CD4+ Th1 T-lymphocytes are believed to be the principal disease mediators, as the Th1 cytokines IFN-γ and IL-2 were highly expressed in the HSK cornea[144] and anti-IFN-γ and anti-IL-2 treatment decreased the incidence and severity of herpetic corneal disease.[145–147] Neutrophils and antigen-presenting cells may also play central roles in HSK pathogenesis.[148, 149] In mice exposed to HSV after a corneal scratch, DMF therapy reduced corneal infiltration of lymphocytes, polymorphonuclear leukocytes (PMNs), and macrophages and decreased the severity and incidence of stromal keratitis.[150, 151] Additional studies of these mice demonstrated that DMF treatment increased the expression of Th2 cytokines IL-4 and IL-10 in lymphocytes cultured from the spleen, although no changes were seen in expression of the Th1 cytokines IFN-γ and IL-2.[151] Thus, while Th1 cytokines are associated with HSK progression, Th2 cytokines are consistently associated with improvement.[151–153] Even though DMF treatment improved outcomes in these HSK mouse studies, DMF had no effect on viral titers, HSV antibody production, or HSV antigen-specific T cell proliferation.[151] These data demonstrate that FAEs have therapeutic efficacy in treating virally-induced inflammation and immune cell infiltration, and that these effects likely result from direct modulation of the immune response rather than interference with virus replication.

VI. FAEs AS ADJUNCTIVE THERAPY FOR HIV INFECTION

A. HIV Systemic Disease

Human immunodeficiency virus type 1 (HIV-1) infection of cells of the immune system (helper T-lymphocytes, macrophages, and dendritic cells) results in profound immunosuppression as well as chronic immune activation. Untreated HIV infection is characterized by high levels of viremia, low levels of CD4+ T-lymphocytes, and subsequent progressive failure of the immune system, resulting in life-threatening opportunistic infections and/or cancer and death. With the widespread use of highly active antiretroviral therapy (HAART) or combination antiretroviral therapy (cART) as such therapy is now called, the long-term survival of individuals living with HIV/AIDS has dramatically increased. As of 2006, the 6-year survival rate for cART-treated HIV infected individuals was 90%.[154] Today, a 20 year-old individual with HIV infection and starting cART is now expected to live into his or her 60s.[155]

1. Persistent Systemic Immune Activation in HIV/AIDS: A Target For Adjunctive Immunosuppressive Therapy—Despite cART providing a significant reduction in morbidity and mortality in HIV-infected individuals, life expectancy is still reduced, particularly in those who begin cART after becoming immunosuppressed (CD4 T-lymphocyte counts < 200 cells/μl).[156–160] A significant risk factor for increased mortality and end-organ diseases in cART-treated individuals is chronic immune activation,[161] which is thought to result from the effects of increased microbial translocation across the damaged gastrointestinal tract (reviewed in[162]). In HIV-infected humans and simian immunodeficiency virus (SIV)-infected macaques microbial translocation across the gut results from several events at the gut mucosal barrier: *i)* severe depletion of mucosal CD4+ T lymphocytes, *ii)* mucosal immune activation and persistent inflammation, *iii)* structural damage to the intestinal epithelium, and *iv)* migration of enteric microbial products into the local mesenteric lymph nodes and extraintestinal sites through the portal and systemic circulation.[162] Among translocated microbial products is lipopolysaccharide (LPS),[162–164] which, upon entering the systemic circulation, interacts with LPS-binding protein (LBP) and then facilitates binding to the monocyte CD14 receptor and toll-like receptor 4 (TLR4). These events then lead to NF-κB activation, cytokine production, and associated immune activation events.[165, 166]

Enhanced immune activation is a consistent observation in both HIV-infected humans and SIV-infected macaques,[167–175] and immune activation of T-lymphocytes and monocytes and associated inflammation are thought to drive HIV pathogenesis.[163, 164, 176–184185, 186187, 188] Elevated plasma levels of IL-6, D-dimer, C-reactive protein (CRP), and fibrinogen are strongly associated with HIV/AIDS mortality.[189, 190] Monocyte/macrophage activation is associated with elevated blood levels of LPS, soluble CD14 (sCD14), and numbers of CD14+/CD16+ monocytes.[182, 191] CD16+ monocytes are more permissive for HIV infection than CD16− monocytes,[192] and circulating CD14+/CD16+ monocytes levels are correlated with increased risk of disease progression.[191] Elevated plasma LPS from gut bacteria translocation can increase the circulating CD16+ monocyte population.[193] LPS is also thought to activate T-lymphocytes in HIV-infected individuals through interactions with TLR4, resulting in effector T-lymphocyte sequestration in lymphoid tissues and T-lymphocyte turnover.[194] The increased T-lymphocyte turnover associated with generalized immune activation could increase the proliferative generation of new memory CD4+ T lymphocytes, which provide new targets for HIV replication and thus promote disease progression, as defined by the endpoints of death, AIDS, CD4+ T lymphocyte counts, and plasma viral load.[162, 195] Depletion of both CD4+ and CD8+ T-lymphocyte populations, which is strongly associated with disease progression,[196] occurs in late stages of disease and is associated with and proposed to be caused by immune activation.[197, 198]

In addition to increasing plasma levels of LPS, HIV can induce immune activation of monocyte/macrophages through direct effects of infection or through the release of factors that can interact with bystander uninfected monocyte/macrophages. For example, the HIV envelope glycoprotein gp120 is shed from virions and can transduce signals in monocytes when presented as a soluble protein or as a component of the virus particle even when presented on non-infectious virions (as in plasma *in vivo*).[199, 200] Gp120 interacts with non-infected, bystander monocytes/macrophages and activates intracellular pathways that lead to monocyte/macrophage immune activation.[199, 200] Other factors released from HIV-infected macrophages, such as TNFα and other proinflammatory cytokines, can also induce bystander cell immune activation.[201–203]

Thus, as systemic immune activation is driven by HIV replication, suppression of HIV replication with cART significantly dampens such immune activation; however this suppression is incomplete.[162, 163, 178, 180, 181, 204–208] The persistence of immune activation despite suppression of HIV replication to undetectable levels remains a major obstacle to preventing further disease progression in cART-treated HIV infected individuals. Successful therapeutic targeting of persistent immune activation has now been proposed as a critical goal for further improving long-term survival, lowering risk of associated end-organ diseases, and improving quality of life in HIV-infected cART-treated individuals.[162, 195]

2. Systemic Oxidative Stress in HIV/AIDS: A Target For Adjunctive Antioxidant Therapy—HIV infection can induce systemic oxidative stress[209–212] through both chronic immune activation[213–215] and direct effects of HIV proteins.[216–219] Increased oxidative stress in HIV-infected individuals was first suggested after confirmation of diminished levels of reduced glutathione in plasma, lymphocytes, PBMCs, and monocytes isolated from such individuals.[220–222] These early findings were supported by later studies demonstrating reduced levels of thioredoxin (a thiol antioxidant) in HIV-infected cells[223] and elevated serum levels of the lipid peroxidation products malondialdehyde[224, 225] and lipid hydroperoxides[226] in HIV-infected individuals. Moreover, the HIV proteins gp120,[216, 219, 227–230] Vpr,[218, 231] and Tat[217, 219] have been directly implicated in the induction of cellular oxidative stress. Oxidative stress in turn can drive NF-κB-driven HIV replication[232–234] and inflammatory cytokine release,[232, 235–239] thus perpetuating chronic systemic immune activation and disease progression in HIV-infected individuals.

Furthermore, *in vivo* markers of oxidative stress correlate with systemic disease progression in HIV-infected individuals[240–242]. One study showed that glutathione deficiency in CD4+ T-lymphocytes from HIV-infected patients was associated with markedly increased mortality.[243] These findings implicate oxidative stress in HIV disease pathogenesis and mortality and highlight the potential for adjunctive antioxidant therapies to ameliorate disease progression in cART-treated patients.

3. FAEs as Candidate Adjunctive Therapy for Systemic HIV disease in cART-Treated Individuals—The FAEs, and specifically the oral DMF preparations (BG-12/Tecfidera™, Fumaderm®), are attractive candidates as adjunctive agents for suppressing chronic immune activation, oxidative stress, and associated HIV disease progression and comorbidities in cART-treated individuals (reviewed in Figure 2). To date, no *in vivo* or clinical studies have examined the efficacy of FAE therapy in HIV infection, however the dual anti-inflammatory and anti-oxidative mechanisms of FAEs suggest potential potent systemic efficacy. FAEs have been studied in *in vitro* models of HIV macrophage-mediated neurotoxicity where they have shown promising results. The CNS penetrance of MMF and the demonstrable suppression of CNS inflammation in BG-12-treated multiple sclerosis patients are especially appealing for targeting persistent CNS inflammation and oxidative stress in such individuals (see section VI.B. HIV CNS Disease).

a. FAEs as Suppressers of Systemic Immune Activation in HIV/AIDS: Through inhibition of the NF-κB signaling, which regulates cytokine and chemokine signaling, oral DMF therapy might provide an additional suppressive effect on the chronic immune activation in cART-treated patients. This prediction is supported by the efficacy of oral DMF-formulations (BG-12/Tecfidera™ and Fumaderm®) in limiting inflammation and immune cell infiltration in multiple sclerosis and psoriasis.[2, 3, 8–10, 103–106, 129] Suppression of chronic immune activation will likely improve long-term survival, lower risk of associated end-organ diseases, and improve quality of life in HIV-infected cART-treated individuals.[162, 195] The glucocorticoid prednisolone, a potent immunosuppressant, lowered systemic immune activation in both untreated and cART-treated patients[244] and postponed CD4+ T-lymphocyte count decreases for a median of two years in untreated HIV-infected patients.[245, 246] Prednisone, the precursor to prednisolone, inhibited monocyte TNFα production without affecting T-lymphocyte antigenic responses.[247] However, the profound side effects of glucocorticoid therapy make its long-term use unattractive as adjunctive therapy. In a small retrospective study, addition of the immunosuppressant cyclosporine to cART therapy during primary HIV-1 infection restored CD4+ T-lymphocytes to normal levels (both percentage and absolute numbers) and adjunctively treated patients maintained higher CD4+ T-lymphocyte levels than those in patients taking cART alone.[248] In this study, cyclosporine adjunctive therapy did not significantly affect virus-specific CD8+ or CD4+ T-lymphocyte responses or viral load.[248] However, another study of the effects of cyclosporine treatment during acute and early HIV-infection in 48 subjects demonstrated no significant improvement in CD4+ T-lymphocyte counts or other markers of disease progression.[249] Notably, cyclosporine has shown limited efficacy in multiple sclerosis,[250–253] in direct contrast to the strong and consistent efficacy reported for the immune modulator BG-12/Tecfidera™,[2, 3] suggesting DMF therapy may similarly prove more effective in HIV-infection. The central role of chronic immune activation in disease progression in cART-treated individuals coupled with these promising findings demonstrating a delayed disease progression with suppression of immune activation strongly supports further exploration of immunomodulatory therapy for the treatment of HIV infection. The anti-inflammatory effects of DMF in cell lineages relevant to HIV-infection coupled with its effectiveness in the chronic inflammatory diseases multiple sclerosis and

psoriasis, makes it a promising adjunctive therapy for improving morbidity and mortality in cART-treated HIV-infected individuals.

b. FAEs as Possible Protectors of the Intestinal Mucosal Barrier in HIV/AIDS: Chronic immune inflammation is believed to occur primarily as a result of microbial translocation across the damaged gastrointestinal tract,[162] as described above. Beyond direct anti-inflammatory effects on immune cells, FAE therapy might ameliorate chronic immune activation through decreasing microbial translocation by several effects: *i)* reversing or halting the depletion of mucosal CD4+ T-lymphocytes, *ii)* limiting mucosal immune activation and inflammation, and *iii*) preventing structural damage to the intestinal epithelium. Through inhibition of NF-κB activity in mucosal lymphocytes and other mucosal immune cells, FAEs could dampen mucosal immune cell activation thereby limiting mucosal inflammation. This decreased inflammation could reduce immune activation-induced T-lymphocyte apoptosis.[254] Recent *in vitro* and *in vivo* mouse studies suggest that inducers of the Nrf2-dependent ARE can protect intestinal mucosa from inflammation-associated oxidative stress and injury and reduce the associated invasion of anaerobic bacteria into the mucosa.[43, 255–259] Therefore, oral DMF through induction of the ARE might limit microbial translocation across the intestinal mucosa and through NF-κB inhibition promote gut immunity, thereby preventing the primary cause of chronic systemic inflammation in HIV-infected individuals.

c. FAEs as Suppressors of Systemic HIV Replication: The ability of DMF and MMF to modulate NF-κB signaling and cellular pathways of cytokine production, particularly of TNFα, suggests the possibility of associated effects on replication of HIV in immune cells. Increased nuclear translocation of NF-κB, through immune activation including TNFα stimulation,[232, 260, 261] drives HIV gene expression from the HIV long terminal repeat (LTR).[262, 263] Therefore, FAE-driven inhibition of NF-κB nuclear translocation and DNA binding might further limit HIV-replication *in vivo*. Potent inhibition of HIV replication by DMF and MMF pre-treatment in primary human monocyte-derived macrophages has been demonstrated *in vitro*.[54] The effect of FAEs on HIV replication in T-lymphocytes, the primary targets of HIV infection, has not been reported. In addition, modification of the oxidative state of immune cells such as increasing glutathione has been shown to interfere with HIV particle assembly, infectivity, and release,[233, 264] which suggests another possible inhibitory effect of FAEs on the HIV life cycle.

d. FAEs as Suppressors of Oxidative Stress in HIV/AIDS: In addition to markers of immune activation, markers of oxidative stress are consistently elevated and associated with disease progression in HIV-infected patients. This role of oxidative stress and glutathione depletion in HIV systemic disease pathogenesis and mortality served as the rationale for treatment of HIV-infected patients with various direct antioxidants, including N-acetylcysteine[243, 265–268] and selenium.[269–271] The largest selenium clinical trial was a randomized controlled trial of 262 HIV-infected patients (192 receiving ART) that reported that nine-months of selenium supplementation resulted in a significant increase in CD4+ T-lymphocyte count and a decrease in viral load.[271] Similar effects on increasing CD4+ T-lymphocyte counts and decreased viral loads were seen in two of the N-acetylcysteine studies.[267, 268] These trials suggest that antioxidant therapies have the potential to modulate HIV disease progression. However, numerous studies suggest that N-acetylcysteine,[272–274] selenium,[275] and other direct antioxidants[276–278] actually suppress the endogenous Nrf2-driven ARE (a pro-oxidative effect), likely due to their direct suppression of oxidative stress, which serves as the main inducer of the Nrf2 translocation and subsequent ARE induction. Furthermore complicating their clinical usefulness, direct antioxidants are expended to elicit their antioxidant effects and thus are often short-lived and need to be replenished

frequently.[279] Therapies that induce sustained activation of the endogenous ARE might provide greater protection against oxidative stress than direct antioxidants due to sustained increased expression of multiple antioxidant effector proteins.

The monoamine oxidase B inhibitor selegiline, which had been shown decrease oxygen free radicals and enhance the expression of antioxidant enzymes superoxide dismutase and catalase,[280–282] has been used to attempt to increase dopaminergic neurotransmission and reduce neuronal injury caused by oxidative stress in Parkinson's and Alzheimer's Disease.[283, 284] In addition, selegiline has been shown to activate the Nrf2 pathway in neuronal cell lines.[285] Despite the success of selegiline in other neurocognitive diseases and the evidence that selegiline may induce the ARE and limit oxidative stress, a 24-week clinical trial of transdermal selegiline therapy (two doses) with a 24-week open-label extension in HIV-infected patients failed to show neurocognitive improvement or positive changes in brain or CSF biomarkers of oxidative stress.[286–288] The reasons for the failure of selegiline therapy to achieve positive outcomes in this trial are unclear. The 24-week treatment duration was relatively brief and each treatment arm, including placebo, showed no neurocognitive deterioration over 24 weeks of open-label follow-up. Some investigators have suggested that augmenting dopaminergic signaling could enhance HIV infection of macrophages and promote neuropathological disease progression in simian immunodeficiency virus (SIV)-infected macaques.[289, 290]

Despite the clinical trial failure of transdermal selegiline, compelling evidence supports oxidative stress as a major driving force in HIV neuropathogenesis. Furthermore, the partial clinical efficacy of direct antioxidants (N-acetylcysteine, Selenium) strongly supports further study of ARE-inducing therapies such as DMF for disease suppression in HIV infected individuals.

e. Potential of FAEs in Treating Systemic HIV-Associated Comorbidities: Despite use of cART therapy, HIV-infected individuals have an increased risk of progressive dysfunction of major organs. Such HIV disease progression can involve the central nervous system (brain/cognition, see section VI.B HIV CNS Disease; spinal cord/myelopathy), peripheral nerves (neuropathy), heart (atherosclerosis, heart failure), liver (cirrhosis, hepatocellular carcinoma), kidney (nephropathy, glomerulonephritis/sclerosis, tubulointerstitial nephritis), and bone (osteopenia, osteoporosis) (reviewed in[291–293]). In these comorbidities, inflammation and possibly the associated oxidative stress are thought to play a significant role.

Cardiovascular Disease: HIV-infected patients have increased risk of atherosclerosis, myocardial infarction, heart failure, and other vascular diseases.[294, 295] Increased serum levels of several markers of inflammation strongly predict cardiovascular disease and mortality.[296–298] Although HIV-infected cART-treated individuals are at lower risk for cardiovascular disease than HIV-infected individuals not receiving cART, they are nonetheless at higher risk than the general population. Risk factors for cardiovascular disease in cART-treated individuals include low-level virus replication, chronic immune activation associated microbial translocation, monocyte activation, and oxidative stress (reviewed in[299]), each of which is a potential target of DMF therapy. Atherosclerosis in particular is driven by persistent inflammation, macrophage and T-lymphocyte infiltration, endothelial cell activation, and oxidative stress.[300, 301] Furthermore, studies of transgenic mice expressing HIV Tat, gp120, and Nef suggest that expression of these HIV-1 proteins, independent of viral infection, can induce cardiac damage through oxidative stress.[228] Such damage is associated with elevated cystine/cysteine ratios and altered glutathione metabolism in cardiac muscle.[228] Similarly, cardiac tissue from Tatexpressing transgenic mice showed decreased glutathione levels, mitochondrial damage, and cardiomyopathy.[302]

Thus, the ability of DMF and MMF to decrease inflammation, immune cell activation and invasion, endothelial cell activation, and injury due to oxidative stress suggest that DMF formulations could decrease the elevated risk of cardiovascular events in cART-treated individuals.

Bone Disease: Osteopenia and Osteoporosis: A recent meta-analysis showed that the prevalence of osteopenia and osteoporosis in HIV-infected individuals was more than three times higher than that in uninfected controls.[303] This could reflect effects of chronic inflammation and associated increased bone resorption[304] as well as HIV-driven (and potentially cART-driven) increases in osteoclast activity.[305] DMF therapy, through limiting systemic inflammation and viral replication, could potentially reduce these pro-osteoclast signals. One such signal, NF-κB activity, regulates osteoclast differentiation and the inflammatory cytokine TNFα that induces bone loss through stimulation of osteoclasts.[306–308] Therefore, DMF therapy through inhibition of NF-κB and TNFα release from immune cells could have further efficacy in decreasing osteoclast activity.

Hepatic and Renal Disease: HIV-infected individuals also have increased risk of both kidney[309–311] and liver[311–313] disease associated with viral replication, low peripheral CD4+ T-lymphocyte count, and the use of certain antiretroviral drugs.[314–319] Given these correlations among renal and liver disease, viral replication (despite cART), and T-lymphocyte counts, DMF therapy could potentially ameliorate HIV-associated liver and kidney disease.

In summary, DMF therapy in HIV-infected patients could reduce disease progression by limiting systemic immune activation and associated oxidative stress. Through induction of the Nrf2/ARE and inhibition of NF-κB, DMF therapy could systemically: *i)* reduce immune cell activation and cytokine release, *ii)* prevent leukocyte tissue infiltration; and *iii)* inhibit HIV infection and replication. Each of these effects has been demonstrated in published studies examining DMF. In addition, suggested possible effects of DMF therapy include the following: *i)* limiting intestinal mucosal barrier damage and associated microbial translocation, *ii)* reducing HIV-associated organ comorbidities, and *iii)* limiting oxidative stress (reviewed in Figure 2). Thus, there is much promise for the use of oral DMF formulations as adjunctive therapy for systemic disease progression and comorbidities in cART-treated HIV-infected individuals.

B. HIV CNS Disease

In addition to systemic inflammation and oxidative stress, HIV infection is also associated with persistent inflammation and oxidative stress within the CNS compartment. Because HIV infection is associated with neurocognitive dysfunction even with individuals who demonstrate complete or nearly complete suppression of HIV replication with cART, adjunctive therapy for neuroprotection is clearly needed in HIV-infected individuals. HIV infection causes varying degrees of cognitive, motor, and behavioral deficits collectively known as HIV-associated neurocognitive disorders (HAND) in up to 50% of cART treated individuals.[320–324] HAND consists of three sub-classifications that span a neuropsychological spectrum of impairment, from asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND) to HIV-Associated Dementia (HAD), the most severe form of HAND. cART has decreased the prevalence of HAD,[325–327] however, a significant proportion of patients on ART (30–50%) continue to develop neurocognitive impairments, despite reduced plasma viremia, improved immunological parameters, and decreased progression to AIDS.[138, 326, 328–337] A recent study shows a significant increase in the prevalence of the milder forms of HAND in the cART era.[330] The high prevalence of HAND and other neurologic manifestations of HIV-infection despite the introduction of

cART underscores a critical need for adjunctive therapies that target the persistent inflammation and oxidative stress within the CNS compartment.[338–343]

1. Macrophages/Microglia are Central Mediators of HAND Neuropathogenesis—Systemic effects of HIV infection are likely driven by HIV replication in CD4+ T-lymphocytes, while CNS effects of infection are predominantly driven by HIV infection of macrophages/microglia. HIV entry into the CNS occurs early in infection,[344–347] with subsequent productive replication in the brain occurring primarily within perivascular monocyte-derived macrophages (MDMs) and microglia, and restricted, non-productive replication in astrocytes.[348–351] Persistent CNS HIV infection drives immune activation of resident macrophages/microglia, pervasive reactive astrocytosis, perivascular inflammation and infiltration of monocytic cells,[352] which can result in HIV-encephalitis (HIVE), particularly in individuals not receiving cART.[353] The introduction of cART has decreased morbidity/mortality of HIV infection, the severity of neurocognitive impairment and associated neuroinflammation in HAND, and the prevalence of encephalitis.[354–359] Despite these beneficial effects of cART, neuroinflammation and neuropathological damage persists,[354–358, 360, 361] and persistent systemic and CNS markers of monocyte/macrophage activation predict neurocognitive impairment,[362–370] even in individuals with excellent virological suppression.[371–377] Moreover, the clinical severity of HAND correlates more strongly with monocyte infiltration and MDM/microglia activation than with CNS viral antigen load or number of HIV-infected cells in the brain.[377–381] In summary, current research highlights the central role of macrophages/ microglia and persistent neuroinflammation in HAND in individuals receiving cART.

2. Macrophages and Microglia Produce HAND-associated Neurotoxins—The neuropathogenesis of HAND has been associated with decreased CNS neuronal synaptic and dendritic density,[380, 382, 383] neuronal apoptosis and necrosis,[379, 384–386] and altered neuronal physiology,[387–395] linked to the aforementioned inflammation and oxidative stress. This neuronal dysfunction is likely a consequence of neurotoxins released from HIV-infected MDM (HIV-MDM) and immune activated MDM/microglia and astrocytes.[396–399] Our laboratory and others have demonstrated that a major component of HIV-MDM neurotoxins are small (<3 kDa), heat-stable, protease-resistant excitotoxins that act through N-methyl-D-aspartate-receptor (NMDAR) activation, a finding supported by studies in animal models of HIV neurotoxicity.[400–402] Many candidate excitotoxins released from HIV-MDM have been described including glutamate,[403] quinolinic acid,[404, 405] NTox,[406] platelet activating factor,[407] TNFα,[408] and the viral proteins gp120[409, 410] and Tat[402, 411, 412] among others. HIV-infected individuals express increased levels of glutamate,[413–415] quinolinic acid,[416, 417] platelet activation factor,[407] TNFα,[418] and other excitotoxins in their CSF, which correlate with increased severity of HAND and neuroinflammation. Many of these neurotoxins released from HIV-MDM also dysregulate astrocyte function, particularly glutamate homeostasis.

Proper functioning of glutamate uptake and metabolism by astrocytes is vital to prevent glutamate-dependent excitotoxicity as astrocytes are the major regulator of glutamate in the brain.[419, 420] Astrocyte control of extracellular glutamate is regulated through multiple mechanisms including direct uptake of glutamate, Ca^{2+}-dependent release of glutamate, and catabolism of glutamate by glutamine synthetase.[419, 420] Each of these processes can be perturbed through the actions of HIV coat protein gp120,[421–424] TNFα,[425–428] arachidonic acid,[421] prostaglandins,[429] reactive oxygen species,[430] and associated neuroinflammation,[420] each of which is also associated with HIV replication within CNS macrophages and microglia. This further emphasizes the link between inflammation, oxidative stress, and neurodegeneration in HIV CNS infection. Accordingly, the identification of endogenous pathways that regulate HIV-MDM production of neurotoxins

and factors that result in astrocyte dysfunction will provide novel therapeutic targets for ameliorating neurodegeneration and neurocognitive impairment in HAND.

3. Macrophage/Microglia-Associated Oxidative Stress in HAND—HIV infection can induce CNS oxidative stress[235, 431–433] through chronic immune activation[213–215] and direct effects of HIV proteins. The HIV viral proteins gp120,[216, 219, 434] Vpr,[218, 435] and Tat[217, 219] have been directly implicated in the induction of oxidative stress in CNS-relevant cell types. Oxidative stress drives NF-κB-driven HIV replication,[232–234] inflammatory cytokine release,[232, 235–239] and neurotoxin production.[236, 433, 436–440] Furthermore, *in vivo* markers of oxidative stress correlate with neurocognitive impairment[235, 439, 441] as well as systemic disease progression[240–242] in HIV-infected individuals. Protection against oxidative stress is provided by the ubiquitous ARE pathway, which is the endogenous cellular antioxidant pathway. The ARE response is driven by the Nrf2 transcription factor, and gp120-induced oxidative stress and inflammation in astrocytes was reported to be significantly higher when Nrf2 expression was suppressed by siRNA.[236] The expression profiles of Nrf2 and its ARE effector proteins in the CNS of patients with HAND has not been reported. Finally, in addition to its role in HAND, oxidative stress has been implicated in the pathogenesis of other neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and Huntington's disease,[438, 442–450] which emphasizes the broad potential value of developing effective CNS therapies against oxidative stress.

4. FAE as Candidate Adjunctive Therapy for CNS Disease in cART-Treated Individuals—As discussed, the oral DMF formulation BG-12/Tecfidera™ decreased relapse rates and associated neuroinflammation in patients with multiple sclerosis in two independent Phase III clinical treatment trials.[2, 3] These studies clearly demonstrate efficacy of oral DMF-treatment in the CNS and its efficacy against neuroinflammation and oxidative stress may provide important adjunctive therapy for HIV-infected patients to prevent and treat HAND.

a. FAEs as Inhibitors of HIV Viral Infection in Monocytes and Macrophages: Pretreatment with DMF and MMF decreased HIV infection and TNFα secretion in HIV monocyte-derived macrophages (HIV-MDM), likely due in part to inhibition of NF-κB nuclear translocation and DNA binding.[54] It is well established that TNFα exposure increases HIV replication through increased nuclear translocation of NF-κB,[260, 261] which drives HIV gene expression from the HIV long terminal repeat (LTR).[262, 263] However, in addition to decreasing autocrine effects of TNFα secretion, there are other possible NF-κB modulating effects of DMF and MMF associated with oxidative stress in HIV-MDM. Oxidative stress has been shown to drive HIV replication,[232–234] likely through NF-κB activation,[33–36] and Nrf2 nuclear translocation and activation of the ARE have been shown to suppress NF-κB (described above).

DMF and MMF induce activation of the ARE and suppress HIV infection at concentrations that are consistent with CSF MMF concentrations *in vivo* (4.4 μM).[70] However, inhibition of NF-κB may require higher DMF and MMF concentrations (>15 μM),[54] which suggests other ARE-mediated, NF-κB-independent effects of DMF and MMF on HIV infection. These effects could include suppression of HIV entry into monocytes and macrophages and disruption of virion assembly and release from infected cells. It has been reported that antioxidants can decrease the stability of CXCR4 and CCR5 mRNA transcripts in human monocytes.[451] Because CCR5 and CXCR4 are the major cellular co-receptors for HIV, such antioxidant effects of DMF and MMF could limit HIV entry into monocytes and macrophages. Furthermore high intracellular glutathione levels in macrophages were associated with defective HIV particle assembly and decreased virion infectivity and release.[233] Thus, DMF and MMF activation of the ARE may limit HIV infection of

monocytes and macrophages at several steps in the HIV life cycle (entry, replication, and particle assembly).

b. FAEs as Inhibitors of Macrophage Neurotoxin Release: One consequence of HIV infection and/or immune activation of macrophages and associated inflammation is the production and release of soluble neurotoxins. Beyond promoting HIV-replication, elevated TNFα levels associated with immune activation increase monocyte entry into the brain and drive associated inflammatory cascades; one consequence is the production and release of soluble neurotoxins from macrophages, microglia, and astrocytes.[452] Activation of the ARE pathway decreases macrophage and microglia activation,[54, 453–456] probably through ARE-mediated inhibition of NF-κB signaling. Work from our laboratory demonstrated that DMF and MMF treatment reduces neurotoxin release from HIV-MDM and associated neuronal death in an HIV neurotoxicity model system.[54] We further demonstrated that the decrease in HIV-MDM neurotoxin release was partly dependent on the ability of DMF and MMF to induce the expression of the Nrf2/ARE effector and cytoprotective protein heme-oxygenase-1 (HO-1).[54] HO-1 is the inducible, rate-limiting enzyme that degrades pro-oxidative and cytotoxic heme to bilirubin and carbon monoxide, each of which has well-documented antioxidant and antiinflammatory effects.[54, 457–460] We showed that HIV-infection of MDM in vitro drastically decreases HO-1 protein expression and that induction of HO-1 in HIV-MDM lowered neurotoxin production independent of viral replication; in contrast, inhibition of HO-1 enzymatic activity in HIV-MDM increased neurotoxin production.[54] These data strongly suggest that HO-1 suppression in HIV-MDM plays a pivotal role in macrophage-mediated neurotoxin production during HIV infection and that rescuing this suppression with DMF or MMF might suppress neurodegeneration in HAND.

c. FAEs as Modulators of Immune Cell CNS Infiltration and Blood Brain Barrier Integrity: In addition to suppression of MDM activation and neurotoxin production, DMF and MMF reduced monocyte chemotaxis driven by CCL2,[54] thus potentially limiting transendothelial migration of monocytes into the CNS during HIV infection. Less monocyte trafficking into the CNS could limit HIV access to the brain and subsequent neuroinflammation. Complementing this effect, DMF can decrease endothelial cell adhesion molecule (ICAM-1, VCAM-1, and E-selectin) expression, thereby decreasing leukocyte rolling and diapedesis.[66, 67] This could potentially further limit immune cell trafficking into the CNS and its complications in HAND. HIV infection also impairs blood brain barrier (BBB) permeability, possibly through actions of released viral proteins, induction of oxidative stress, or induction of systemic inflammation (reviewed in[461]). Each of these can disrupt the structural integrity of the BBB in part through breakdown of tight junctions, thereby increasing microbial invasion and immune cell infiltration.[461] Recent studies of post-traumatic brain injury[462] and subarachnoid hemorrhage[463] in mice suggested that activation of the Nrf2/ARE antioxidant and detoxifying enzymes preserve BBB and tight junction integrity. Moreover, Nrf2/ARE activation in choroid plexus cells preserved the blood-CSF barrier after oxidative stress injury.[464] Therefore, DMF therapy could further protect the CNS compartment more globally from microbe and immune cell invasion and other systemic insults through direct protection of the BBB and blood-CSF barrier through its antioxidants effects.

d. FAEs as Astrocyte and Neuron Protectants From Inflammation and Oxidative Stress: In addition to macrophages and microglia, astrocytes and neurons are also possible CNS targets for FAEs. DMF has been shown to decrease astrocyte activation and the release of inflammatory cytokines,[69–71] which could further dampen CNS neuroinflammation. DMF treatment also decreased macrophage and microglia activation[55] and associated release of TNFα release[54] and likely other HIV-MDM factors[421–430] through ARE induction, which

have been shown to impair astrocyte glutamate homeostasis and promote glutamate-mediated excitotoxicity. TNFα in particular can suppress astrocyte glutamate scavenging through impairment of their high affinity glutamate transporters, which are critical for regulation of extracellular glutamate levels.[420, 465] Furthermore, TNFα released into supernatants of HIV-infected macrophage cultures can induce nitric oxide synthase and nitric oxide production and release by exposed astrocytes;[466] such a process could amplify CNS oxidative stress and associated injury during HIV infection. Although such possible effects of DMF and MMF on HIV-MDM-mediated astrocyte dysfunction have not been studied, DMF treatment has been shown to directly protect both astrocytes and neurons from oxidative injury and glutamate toxicity through Nrf2/ARE induction.[69–71] Because glutamate mediated excitotoxic injury has been implicated in the pathogenesis of HAND, these studies suggest DMF might project neurons directly from HIV-mediated neurotoxicity as well as indirectly by preventing astrocyte dysfunction.

In summary, DMF therapy in HAND patients could have both direct and indirect neuroprotective effects through inhibition of NF-κB activity and Nrf2/ARE induction in different CNS cell types (reviewed in Figure 2). Direct effects could occur through induction of neuronal cytoprotective antioxidant responses. Indirect effects could occur through DMF/MMF actions in macrophages/microglia, astrocytes, endothelial cells, and choroid plexus cells. Confirmed macrophage effects of DMF and MMF[54] include: *i)* suppressing neurotoxin production; *ii)* limiting HIV infection; *iii)* impairing monocyte chemotaxis; *iv*) inhibiting TNFα release; and *v*) inhibiting NF-κB nuclear translocation. Proposed astrocyte effects include: *i*) inhibiting release of TNFα and other proinflammatory cytokines; *ii)* preserving glutamate scavenging and glutamate homeostasis; *iii)* limiting production of nitric oxide and associated pro-oxidants. Additionally, indirect neuroprotective effects of DMF and MMF could also occur through actions in endothelial cells, which maintain the BBB. Confirmed effects in endothelial cells include: *i)* reducing adhesion molecule expression; and *ii)* promoting BBB structural integrity. Finally, DMF therapy could preserve the blood-CSF barrier integrity through actions in choroid plexus cells. Thus, there is much supporting evidence for the study of DMF as an adjunctive therapy for neuroprotection against HAND in cART-treated HIV-infected individuals.

C. Safety of FAE Immunomodulatory Therapy in HIV-infected Individuals

The clinical safety of long-term use of oral FAE therapy in humans is supported by a lack of clear evidence of serious adverse events after more than 17 years of its widespread use for the treatment of psoriasis, and its recent use in Phase III multiple sclerosis treatment trials involving more than 2600 patients (see section III. Safety and Adverse Events for long term clinical safety data and recent PML case reports). Nonetheless, its use in HIV-infected individuals has not been established, and the potential risks of this application must be considered. Among these concerns is the possibility that immunosuppressive FAE therapy in HIV-infected patients would increase their risk for opportunistic infections, malignancy, acceleration of HIV infection, and mortality.[467, 468] However, potent immunosuppressive therapy has been used successfully in HIV-infected individuals undergoing organ transplantation for nearly two decades, with no significant increase in risk for these complications in comparison with such complications in HIV-negative transplant recipients.[469–472] Several studies have reported that HIV viral loads and CD4+ T-lymphocyte counts were well-maintained after kidney and liver transplantation in HIV-infected patients.[473–475] Moreover, the largest prospective study of cART-treated HIV-infected recipients of kidney transplantation (n = 150) receiving standard immunosuppressive therapy reported one and three year survival rates to be 94.6% and 88.2%[475], respectively, which is not significantly different from current kidney transplant survival rates as reported by the U.S. Scientific Registry of Transplant Recipients.[476]

Furthermore, the increased risk of *de novo* or recurrent malignancy in HIV-infected patients undergoing solid-organ transplantation and subsequent immunosuppressive therapy was low.[477]

Other immunosuppressive drugs including prednisolone[244, 245] and cyclosporine[248, 249] have also been studied in clinical trials in cART-treated HIV-infected patients and these trials revealed no increased risk for opportunistic infections, increased viral load, or disease progression. These studies demonstrate that potent immunosuppressive regimens are generally safely used in cART-treated HIV-infected individuals and they further suggest that DMF formulations could also be safely used in HIV-infected cART-treated individuals.

VII. CONCLUSIONS

DMF formulation therapy reduces inflammation, immune activation, and oxidative stress in numerous cell lineages *in vitro*, particularly cells of the immune system, and such therapy has potent clinical efficacy in psoriasis and multiple sclerosis, likely through limiting inflammation and associated oxidative stress and immune cell infiltration in these diseases. Based on these effects, this review proposes DMF as a potential adjunctive therapeutic in cART-treated HIV-infected individuals for improving morbidity and mortality by ameliorating immune activation and associated microbial translocation, systemic oxidative stress, and HIV-associated comorbidities, particularly HIV-associated neurocognitive disorder (HAND).

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Abbreviation List

AIDS	acquired immunodeficiency syndrome
ARE	antioxidant response element
BBB	blood brain barrier
cART	combination antiretroviral therapy
CCL	CC chemokine ligand
CCR	CC chemokine receptor
CD	cluster of differentiation
CNS	central nervous system
CXCL	CXC chemokine ligand
CXCR	CXC chemokine receptor
DMF	dimethyl fumarate
FAEs	fumaric acid esters
HAND	HIV-associated neurocognitive disorder
HIV	human immunodeficiency virus
HO-1	heme oxygenase-1
HD	Huntington’s Disease

HSK	Herpe Stromal Keratitis
HSV	herpes simplex virus
ICAM	intercellular adhesion molecule
IFN	interferon
IL	interleukin
LPS	lipopolysaccharide
MDM	monocyte-derived macrophages
MEF	monoethyl fumrate
MMF	monomotheyl fumarate
Nrf2	nuclear factor erythroid-2 related factor-2
NF-κB	nuclear factor κB
PBMC	peripheral blood mononuclear cells
TNF	tumor necrosis factor

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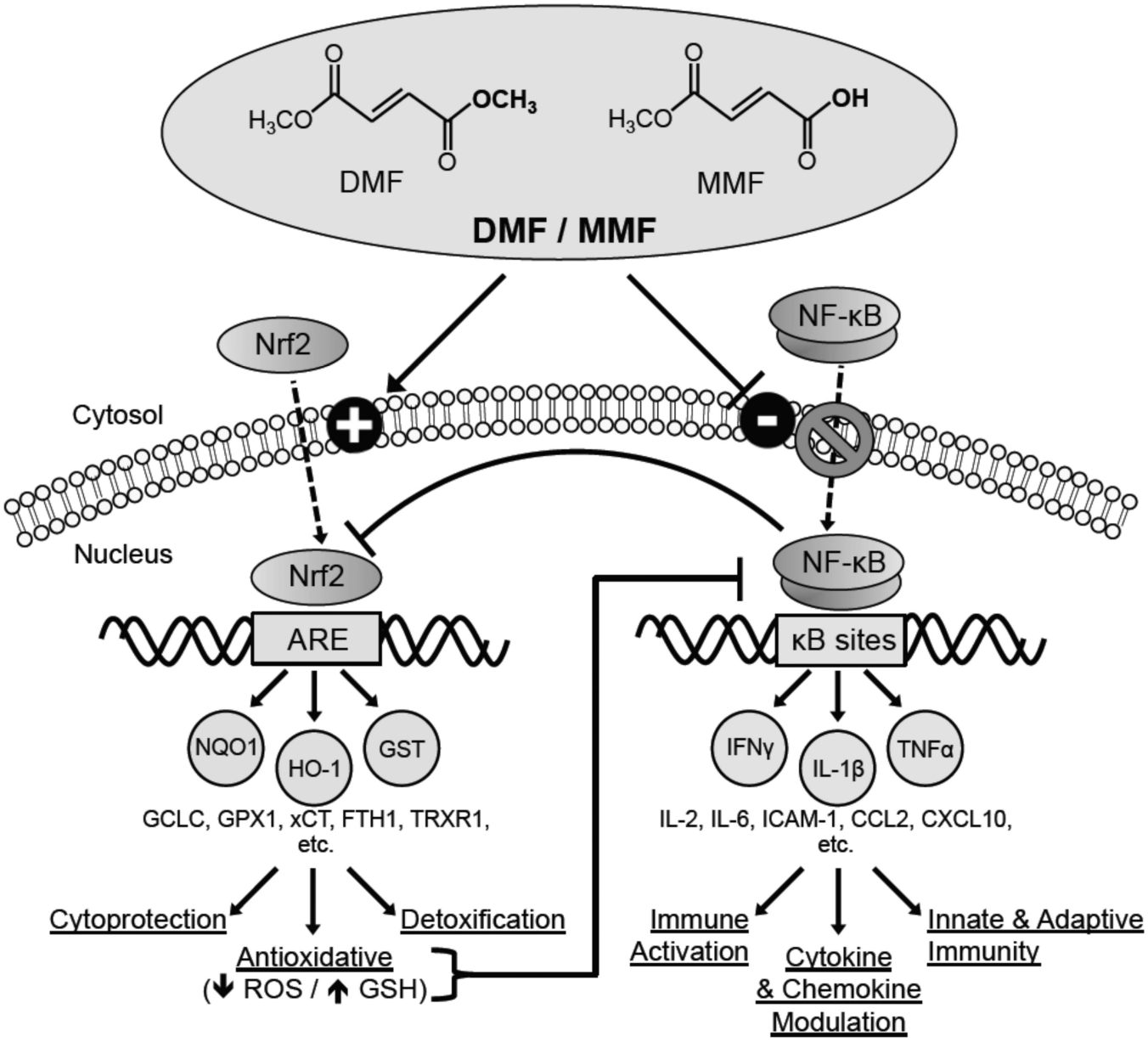

Figure 1.

Effects of the fumaric acid esters (FAEs) DMF and MMF on the Nrf2-dependent antioxidant response and NF-κB pathways. Flat head on a line instead of an arrow head indicates a negative or inhibitory relationship. Abbreviations used: antioxidant response element (ARE), CC chemokine ligand (CCL), CXC chemokine ligand (CXCL), cysteine/glutamate transporter (xCT), dimethyl fumarate (DMF), ferritin heavy chain 1 (FTH1), γ-glutamate cysteine ligase catalytic subunit (GCLC), glutathione (GSH), glutathione peroxidase-1 (GPX1), glutathione S-transferase (GST), heme oxygenase-1 (HO-1), intercellular adhesion molecule (ICAM), interferon (IFN), interleukin (IL), monomethyl fumarate (MMF), NAD(P)H quinone oxidoreductase-1 (NQO1), nuclear factor E2-related factor 2 (Nrf2), nuclear factor κB (NF-κB), reactive oxygen species (ROS), thioredoxin reductase 1 (*TrxR1*), tumor necrosis factor (TNF).

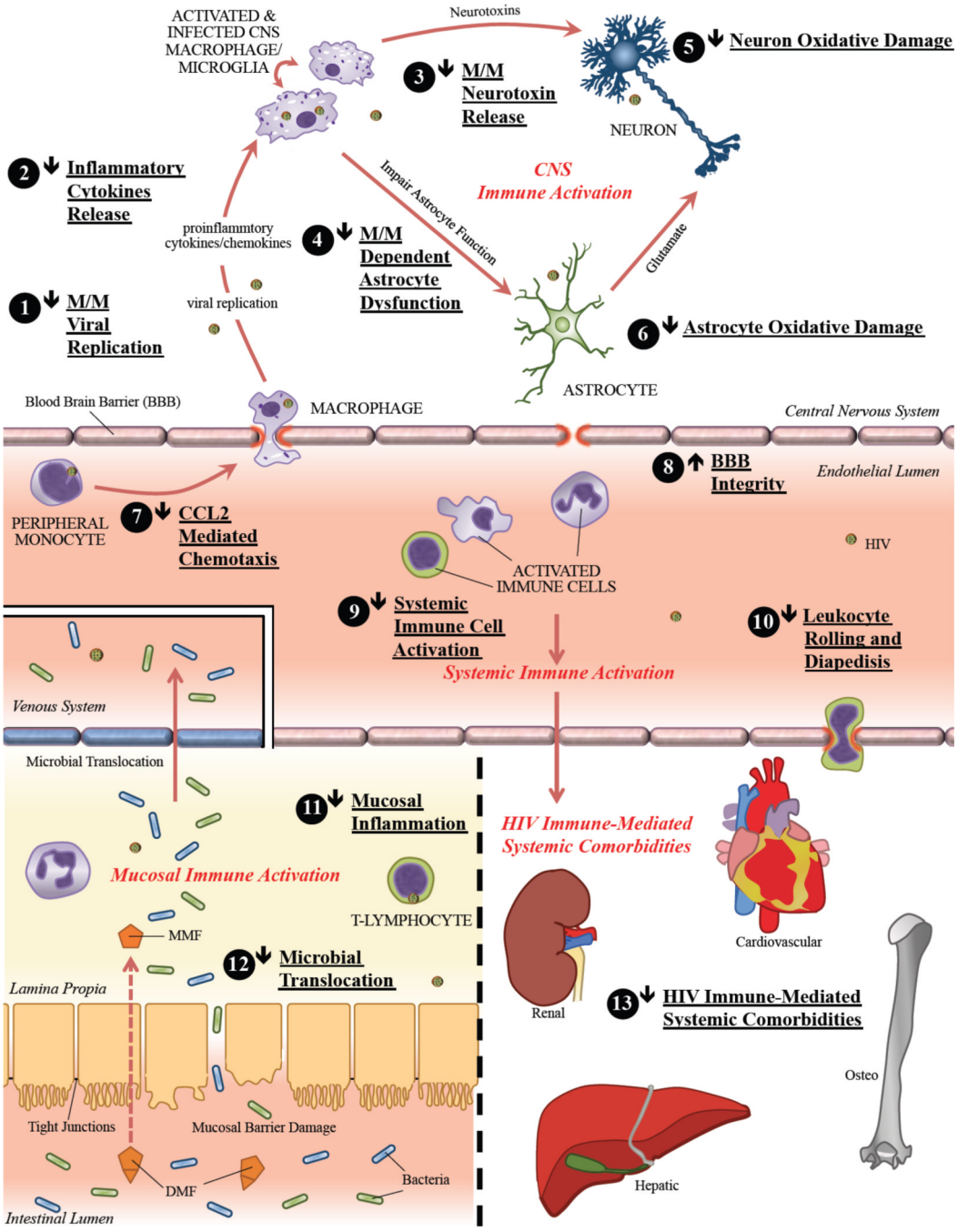

Figure 2.

Potential effects of dimethyl fumarate (DMF) therapy on systemic and CNS HIV-disease pathogenesis. Oral DMF, primarily through its active *in vivo* metabolite monomethyl fumarate (MMF), might have potent anti-inflammatory and anti-oxidative effects (marked by numbers 1 – 13 in figure) in HIV-infected cART-treated individuals thereby limiting both systemic and CNS chronic immune activation and oxidative stress. This could result in decreased HIV-disease progression and associated comorbidities. Abbreviations used: monomethyl fumarate (MMF), dimethyl fumarate (DMF), blood brain barrier (BBB), macrophage/microglia (M/M)

Table 1

Effects of dimethyl fumarate (DMF) and monomethyl fumarate (MMF) on different cell lineages relevant to HIV infection.

Cell Type	DMF/MMF	Cytokine/Receptor Expression changes	Effects	References
T-cells	DMF	↑ IL-4, IL-10 ↔ CCR4, IL-5 ↓ NF-κB DNA binding, INFγ, CXCR3 CXCR10, IL-6, TGFα, CD25, CLA	TH1 → Th2 shift ↓ endothelial rolling, firm adhesion, & tissue infiltration ↓ binding to E-selectin, P-selectin, and VCAM-1	47–51, 53
	MMF	↑ IL-4, IL-5 ↔ NF-κB DNA binding, INFγ, IL-2	Th1 → Th2 shift ↓ dendritic cell differentiation	
PBMCs	DMF	↓ CXCL8,CXCL9, CXCL10	Th1 → Th2 shift ↓ macrophage inflammatory cytokine production ↓ leukocyte rolling	47, 52, 53
	MMF	↑ IL-4, IL-10, IL-5 ↔ INFγ, IL12, IL-2	Th1 → Th2 shift	
Monocyte/Macrophages	DMF	↑ Nrf2 ↓ NF-κB nuclear translocation & DNA binding, TNFα, CCR2	↑ Antioxidant response, ↑ HO-1 ↑ superoxide anion ↓ CCL2-induced chemotaxis	54, 57
	MMF	↑ Nrf2 ↓ NF-κB nuclear translocation	↑ Antioxidant response, ↑ HO-1 ↑ superoxide anion ↓ CCL2-induced chemotaxis	
Dendritic Cells	DMF	↑ IL-10 ↓ NF-κB activity (less free p65), IL-12, IL-6, IL-23	↑ Type II dendritic cells ↓Monocyte dendritic cell differentiation ↓ intracellular glutathione levels	59–63
	MMF	↓ NF-κB activity (less free p65), IL-12, IL-10, TNFα, IFNγ	↑ Type II dendritic cells ↓Monocyte dendritic cell differentiation ↓ effectiveness in stimulating Th1 cytokine production in T cells	
Endothelial cells	DMF	↔NF-κB DNA binding ↓NF-κB nuclear entry, E-selectin, VCAM-1, ICAM-1	↓ TNFα indicated cytokine release ↓ leukocyte rolling and firm adhesion	64–67
	MMF	↔ NF-κB DNA binding, E-selectin, VCAM-1, ICAM-1	?	
Microglia	DMF	↑ Nrf2 expression ↓ IL-1β, IL-6, TNFα, iNOS	↑ Antioxidiant response, ↑ HO-1 ↓ Nitrites	55,56
	MMF	↑ Nrf2	↑ Antioxidant response, ↑ HO-1	
Astrocytes	DMF	↑Nrf2 expression, nuclear entry, and DNA binding ↓ IL-1β, IL-6, TNFα	↑ Antioxidant response, ↑ HO-1 ↑ Viability after oxidative stress	55, 69, 70
	MMF	↑Nrf2 expression, nuclear entry, and DNA binding	↑ Antioxidant response, ↑ HO-1 ↑ viability after oxidative stress (Nrf2-depdent)	
Neurons	DMF	↑Nrf2 nuclear entry ↔ NF-κB nuclear entry	↑ Antioxidant response ↑ viability post oxidative & glutamate toxicity (Nrf2-dependent)	69–71
	MMF	↑Nrf2 nuclear entry	↑ Antioxidant response ↑ viability post oxidative stress (Nrf2-dependent) ↔ viability post glutamate toxicity	