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The Rise and Fall of Efavirenz

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Since its introduction to market in 1998, efavirenz (EFV) has been a cornerstone in highly active antiretroviral treatment regimens and the benchmark for clinical trials evaluating new agents in treatment-naive patients. It was incorporated as a component of the first "one pill, once daily" treatment regimen for HIV infection, Atripla (EFV/emtricitabine/tenofovir [TDF]) (a trademark of Bristol-Myers Squibb Company, Princeton, NJ, USA). Although EFV was considered a first-line HIV treatment option for many years, the most recent update to the Department of Health and Human Services (DHHS) guidelines in April 2015 was historic as it is now considered an alternative agent.[1] In contrast, other guidelines have defined different roles for EFV, with the World Health Organization (WHO) guidelines recommending Atripla as the sole preferred agent for all treatment-naive patients and the guidelines from the Grupo de Estudio de SIDA (GeSIDA) making similar recommendations to the DHHS.[2,3] Although the DHHS and GeSIDA guidelines have taken a stance by lowering the recommendation for EFV on the spectrum of antiretroviral therapy, it opens up discussion for several important clinical practice questions—is there a patient or patient population best suited for an EFV-based regimen relative to the other regimens? Should clinicians change patients currently stable on EFV-based regimens to one of the preferred regimens? This opinion paper reviews these questions.

Despite EFV being relegated to alternative status, it possesses several advantageous characteristics and remains the drug of choice in the nonnucleoside reverse transcriptase inhibitor (NNRTI) class. For example, similar to other NNRTIs, EFV displays a long terminal half-life. This pharmacokinetic benefit resulted in studies demonstrating "forgiveness" in regard to suboptimal adherence and creating the possibility of "drug holidays" for certain patient populations.[4,5]

Efavirenz first gained notoriety among prescribers when it was successfully compared to indinavir (IDV) and later formulated as part of a single-tablet regimen, leading to an accrual of clinical experience.[6] Virologically, the findings of the AIDS Clinical Trials Group 5142 study reinforced the potency of EFV when compared to protease inhibitor (PI)-based regimens.[7] Additionally, simplification studies with EFV-based single-tablet regimens in patients controlled on multitablet regimens indicated durability of virologic suppression and improved adherence.[8,9] Finally, EFV distributes effectively into the cerebrospinal fluid, achieving therapeutic concentrations that could confer additional benefit.[10] The importance of central nervous system (CNS) penetration of antiretroviral therapy continues to be debated, given that this is a sanctuary site for replication, and perhaps evidence will continue to mount suggesting this should be given higher consideration when selecting a regimen.

Despite its clear efficacy in the management of HIV infection, it does have a number of important adverse effects that may limit its use. Although recently debated, EFV remains pregnancy category D, which precludes its use in females of childbearing age.[11] Furthermore, it is fraught with drug–drug interactions due to its inductive and/or inhibitory effects on CYP450 enzymes, thus often complicating other medical management. Despite the possibility of drug holidays in some patients, EFV does have a low-genetic barrier to resistance and poses a concern for patients who struggle with consistent medication adherence. Moreover, transmitted resistance is particularly important for EFV as the K103N mutation, which confers high-level resistance to EFV and other first-generation NNRTIs, is most likely to be transmitted in newly acquired infections.[12] Conversely, PIs and dolutegravir have a higher genetic barrier and are far less likely to display baseline resistance in treatment-naive patients and should be considered in patients who have a history of noncompliance.[13]

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Perhaps the most concerning limitation in the use of EFV is its potential to cause CNS adverse effects, particularly in those with a history of psychiatric illness. Although the package insert suggests the CNS effects of EFV wane over the first month, most patients in practice report experiencing residual effects indefinitely.[14] These CNS effects include, but are not limited to, difficulty concentrating, vivid or abnormal dreams, depression, and possible suicidal ideation. Mollan and colleagues quantified the risk of suicidality associated with patients on EFV to be greater than 2-fold.[15] However, a later study conducted by Bristol-Myers Squibb was unable to reproduce the findings, using data from 2 large insurance databases, and concluded there was no correlation.[16] Finally, some studies suggest that the primary metabolite of EFV is neurotoxic, further emphasizing a "balance" between CNS benefit and limitation of the drug.[17] Another characteristic of EFV that contributes to CNS tolerability is the unique pharmacogenetic profile. The CYP2B6 polymorphism results in greater EFV concentrations observed in patients of African descent compared to other ethnicities.[18-22]

Efavirenz has also found its way into recreational drug use due to its well-known hallucinogenic properties.[23] Anecdotal reports claim that EFV, when crushed and smoked, produces a psychoactive effect similar to lysergic acid diethylamide.[24] "Whoonga" is a mixture of EFV and other illicit drugs that are crushed and smoked and has gained popularity in South Africa.[25,26] Another cocktail, known as "nyoape," is a combination of EFV (or ritonavir), heroin, methamphetamines, and cannabis that is used intravenously.[27] Both cocktails have been reported in South Africa and pose a threat to those taking antiretroviral medications therapeutically as these medications are stolen and sold. Due to its intravenous usage, nyoape has the added complication of being associated with infective endocarditis.[27]

The paradigm shift of transitioning EFV to alternative status is the result of the "Achilles heel" of the drug-tolerability. Efavirenz is considered the gold standard comparator agent in most treatment-naive clinical trials; however, one could also question whether it should continue to be used in this capacity. In the noninferiority trials for recently approved agents such as elvitegravir and dolutegravir, data have continued to accumulate, suggesting EFV was beginning to lose favor in the antiretroviral armamentarium. Many drugs have been compared to EFV and demonstrated noninferiority; however, for the first time, dolutegravir displayed superiority, and most experts agreed that tolerability played a pivotal role in the EFV treatment arm.[28,29] Without question, EFV is efficacious; however, the accumulation of anecdotal reports of the aforementioned adverse effects should cause clinicians to pause and consider the patient's ability to tolerate it, especially relative to other approved regimens with less complications.

Patients who might benefit from EFV include those in resource-limited settings or those in which HIV-associated neurodegenerative disease is thought to be significant. Again drawing from data suggesting drug therapy may also need to target HIV replication in the CNS.[30] It could also be argued that as a single-tablet regimen, it should continue to be utilized to facilitate improved adherence.[8,9,31] Moreover, lower doses may be equally effective with fewer adverse effects based on the findings of the Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1) study. The significance of this finding, especially in the United States, remains to be determined, as at present, the 400 mg dose is not US Food and Drug Administration approved; however, the WHO guidelines will soon include this dose as part of an alternative treatment regimen.[32,33] Cost, while not commonly an issue in the United States due to the AIDS drug assistance programs, may also lead to continued use, as EFV will likely become generic in the near future. In regard to patients already receiving an EFV-based regimen, most experts agree that patients should likely continue the current regimen, especially if the patient is receiving it in a single-tablet combination and maintains virologic control. If patients continue to experience residual adverse effects, consideration should be given to changing to an alternative regimen.

Efavirenz stands to be likely transitioned into a more prominent role in resource-limited settings outside the United States in a similar manner to nevirapine (NVP) and stavudine (d4T), although use of the agent for recreational use continues to be a concern. Regardless of the advantages described previously, patients being treated today have considerably more options that do not carry the same disadvantages of EFV.

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