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The Case for Greater Access for Once-Daily Single Tablet Regimens to Treat HIV Infection in Europe

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INTRODUCTION

In recent decades, the prognosis for those diagnosed with Human Immunodeficiency Virus (HIV) has dramatically improved. Advancements in pharmacotherapies and antiretroviral medications have been paramount in this change. One of the defining innovations was the combination antiretroviral therapies (cART) involving different classes of medications to combat HIV infection. To address the need for patients to ingest multiple pills per day, co-formulated, once-daily fixed-dose combination (FDC) single tablet regimens (STR) soon evolved, significantly mitigating the pill burden associated with a multi-tablet regimen (MTR) [1]. Some of the more popular once-daily FDC STRs today are combinations of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleotide reverse transcriptase inhibitor (NNRTI) such as Atripla® (combining efavirnez, emtricitabine, and tenofovir disoproxil) and Eviplera®/Complera® (combining emtricitabine, tenofovir disoproxil, and rilpivirine), while use of integrase inhibitor-containing STRs such as Stribild® (combining elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil) and Triumeq® (combining dolutegravir, abacavir and lamuivudine) and STRs replacing tenofovir disoproxil (TDF) with tenofovir alafenamide (TAF) are increasingly being used. Although the acquisition costs for STRs are typically higher than the total cost for the separate equivalent components, STRs have been shown to positively impact patient outcomes through improving medication adherence and effectiveness, while being judged as a cost-effective therapeutic option [1]. Despite these findings, the stringent market access for STRs seen across Europe does not reflect their demonstrated clinical and economic benefits. Indeed, Payers and Health Technology Assessment (HTA) decision-makers in the big EU-5 markets have instead enacted policies and issued recommendations making access to these therapies more difficult [2-7].

The convenience benefits associated with STRs have enhanced therapeutic effectiveness and adherence. A recently published meta-analysis by Clay et al (2015) found that after 48 weeks of treatment, significantly better viral load suppression was found in the STR groups in comparison to the MTR group (P=0.0003); in addition, the odds of adherence associated with an STR regimen was found to be 2.37 times higher than with an MTR (P<0.0001) [8]. As higher treatment adherence in HIV has been shown to improve viral load suppression, drug resistance, and survival while increasing patient quality-of-life (QoL), this finding is of considerable importance [1, 8-13]. Finally, among key efficacy and safety domains (including change in CD4 cell count at 48 weeks, tolerability/discontinuation, mortality, and Grade 3 or 4 adverse events), outcomes associated with STR were found to be comparable to MTR [8]. More recently, a prospective multicenter study in Spain and France found that Atripla® was associated with a significantly lower virological failure rate than both an MTR containing the same compounds as Atripla® and other MTRs containing different compounds [14].

STRs are not only associated with benefits in efficacy, adherence, and QoL, but have been demonstrated to be economically attractive as well in comparison to MTRs. Several European studies have looked into the cost-effectiveness and overall annual costs of an STR versus an MTR. Newly diagnosed HIV patients in a Milan hospital, for instance, incurred considerably lower mean annual costs starting on an STR rather than an MTR (€9,213 vs. €14,277) [15]. Another Italian study found that STRs were more cost-effective (more Quality-adjusted Life Years (QALYs)) than a number of MTRs, including tenofovir/emtricitabine plus raltegravir and abacavir/lamivudine plus atazanavir/ritonavir [16]. With some individual HIV drugs increasingly available as generic medications, a debate has en-

sued concerning the possibility of incorporating generics into cART and breaking apart once-daily STRs to realize potential cost savings on the long-term. Sweet et al (2016) developed a simulation model of lifetime health and economic outcomes; STRs had an incremental cost-effectiveness ratio of $26,384 per QALY gained, indicating a good value for money under the normal cost-effectiveness thresholds (adopted by various HTA entities) despite substantial price reductions of generic medications [17].

European Payers and clinical bodies responsible for guideline development in HIV/AIDS have however made access to STRs difficult throughout the major markets largely based on treatment acquisition cost and budgetary impact analysis. For example, in France, HIV guidelines created in 2013 proposed substituting Atripla® with generic efavirenz and generic lamivudine + tenofovir (Viread®), with an argument being made that lamivudine and emtricitabine are clinically indistinguishable (despite evidence demonstrating superiority of emtricitabine over lamivudine in terms of virological efficacy) [2]. Elsewhere, the Lazio region in Italy, in contrast to the evidence-based clinical pathway developed for the Lombardy region, based their HIV treatment pathway on a budget impact assessment of the therapeutic options available, mitigating the role of clinical evidence in their recommendations [3].

In other markets, STRs have been subject to incredible scrutiny from national-level HTA bodies and Payers. In Germany, for instance, the G-BA ruled that Eviplera® only had additional therapeutic benefit for newly-diagnosed patients with a viral load less than or equal to 100,000 HIV-1 RNA copies per milliliter (no additional benefit in previously treated patients) [4]. Similarly, no additional benefit was identified for Stribild® for both treatment-naïve and pretreated patients [5, 6]. In the UK, Stribild® is only nationally commissioned for patients who are unable to tolerate first line efavirenz as a result of its toxicity or poor patient adherence [7].

As the evidence base strongly suggests that patients on STRs are more adherent and may derive greater efficacy benefits than patients on an MTR containing equivalent compounds, European Payer decision-making may not adequately reflect the clinical and economic gains related to an STR, including the potential positive effects of long-term adherence. Despite a higher initial treatment acquisition cost, longer term economic analyses show that STRs are associated with lower annual treatment costs than MTR equivalents and are cost-effective (owing to the cost offsets associated with effective overall disease management and better outcomes) [15-17].

Amidst austerity measures adopted by Payers, HIV physicians in Europe have however been adopting STRs, with almost half of the prescribed HIV regimens being STRs in 1Q2015; two-thirds of the physicians cited 'regimen simplification' as the primary reason for switching patients from conventional MTR to an STR [18].

In arriving at clinical pathways and HTA recommendations, European Payers and other pertinent stakeholders should consider the established evidence substantiating the advantages once-daily STR may provide to patients through enhanced convenience, with the potential to be cost-effective over the long-term. A short-term view based on budget impact could potentially limit the progress being made in improving patient health outcomes. Pharmaceutical manufacturers need to continue to focus on bringing innovative medicines, including more STRs, to the market to increase the armamentarium of cost-effective treatment options, with an eye towards economic sustainability of our healthcare ecosystem. Even though STR adoption has increased in Europe in recent years, there is still work to be done to further improve patient outcomes, increase adherence, and reduce long-term cost burden.

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