REVIEW

# Issues in resistance, adherence, and comparative efficacy of the single-tablet regimen combination of tenofovir, emtricitabine, and efavirenz in the management of HIV-1 infection

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**Abstract:** Atripla is the first once-daily, single-tablet, triple-combination antiretroviral therapy. It is recommended for the initial treatment of the naïve patient with human immunodeficiency virus-1 (HIV-1) infection in all current guidelines, based on its proven efficacy in numerous head-to-head randomized clinical trials. Not only has it proven efficacy, but the fixed-dose combination, Atripla, has resulted in an improvement in adherence, quality of life, and satisfaction among naïve as well as virally suppressed patients switching from another regimen. Despite the advantages, tolerability issues can arise that are related primarily to the efavirenz component, which is known to cause central nervous side effects such as dizziness, abnormal dreams, and anxiety. Although generally self-limited, these side-effects can lead to treatment discontinuation in the short- or long-term. Based on the observation of neural tube defects in macaque models, and isolated case reports in human fetuses with first trimester exposure, it is rated as Food and Drug Administration pregnancy category D, and considered as contraindicated in the first trimester of pregnancy where alternatives are available. Given the low genetic barrier of each of the individual components, resistance remains an important issue for patients with poor adherence, but is balanced in part by the long half-life of the drugs. Transmitted resistance is described in up to 16% of newly infected patients in population surveys, and is particularly prevalent in men who have sex with men. Minority variants that may impart resistant to efavirenz are not detected with currently used HIV-1 genotype assays, but nonetheless may also be implicated in patients who fail initial treatment. Several single-tablet regimens are recently licensed or in development that will challenge Atripla as the single-tablet first-line option, but none have shown superior efficacy to date.

**Keywords:** Atripla, adherence, HIV, resistance, fixed-dose, efavirenz

## Introduction

Current treatment guidelines for human immunodeficiency virus-1 (HIV-1) therapy in treatment-naïve patients recommend the use of two nucleoside reverse transcriptase inhibitors (NRTIs), combined with a non-NRTI (NNRTI), a ritonavir-boosted protease inhibitor, or an integrase inhibitor.[1–3] Atripla® (Gilead Sciences, Foster City, CA, Bristol-Myers Squibb, New York, NY) is a coformulated fixed-dose tablet containing two NRTIs: 300 mg tenofovir disoproxil fumarate (TDF), 200 mg of emtricitabine (FTC), combined with an NNRTI, 600 mg of efavirenz (EFV).[4] It is the first US Food and Drug Administration (FDA)-approved single-tablet, once-daily regimen, and the United States Department of Health and Human Services (DHHS) guideline-preferred

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treatment of antiretroviral-naïve adults and adolescents with HIV-1 infection.[1] All other recommended first-line treatment regimens involve combinations of agents requiring at least three tablets taken either once or twice a day. Since the introduction of Atripla and its expedited review for approval by the FDA in 2006,[5,6] it has quickly become a popular choice as the initial choice for combination antiretroviral therapy (cART) in treatment-naïve adult and adolescent patients with HIV-1 infection.[7–9] The simplicity and convenience of a once-daily regimen appeals to patients and health-care providers, and has resulted in improved medication adherence, a critical factor in the success of a cART regimen.[10,11] Studies have also shown that once-daily dosing can lead to improved patient satisfaction and quality of life (QoL), and can prolong the durability of the initial cART regimen.[12–14]

## Pharmacokinetics and mechanisms of action

An open-label crossover study in 48 patients demonstrated that Atripla provided similar drug levels when compared to the ingestion of its individual components,[15] findings which were confirmed in a second study of 37 patients switching to Atripla.[16] The time to peak plasma concentrations ranges from 1 hour (TDF) to 5 hours (EFV). The plasma half-life is significantly longer for EFV (52–76 hours) compared with TDF (17 hours) and FTC (10 hours).[5,17] The maximum plasma concentration of EFV can be significantly and variably increased when taken with a high-fat meal. In order to obtain reliable serum levels, EFV is recommended to be taken on an empty stomach. Dosing is suggested to be at bedtime in order to minimize the impact of the neurological side-effects of EFV. EFV induces liver cytochrome p450 enzymes 3A4, 2C9, and 2C19 and may result in decreased plasma concentrations of drugs that utilize these pathways. Clearance of EFV is increased with drugs that induce 3A4, such as the rifamycins, and dose adjustment may be required in some cases.[5] A review of drug–drug interactions can be found in a number of recent reviews.[18,19] TDF and FTC are renally cleared, and dose-interval adjustments must be made in patients with a creatinine clearance $< 50$ mL/m^{3}. In this situation, Atripla must be replaced with its constituent components.[5,17]

TDF and FTC are nucleotide and nucleoside analogs, respectively, which inhibit HIV-1 replication via DNA strand termination. EFV is a noncompetitive reverse transcriptase inhibitor that acts by binding to the enzyme at an alternate site to the NRTIs. By doing so it modifies the configuration of the reverse transcriptase rendering it inactive.[20] All three medications are prodrugs that only become active after

enzymatic alteration in the cell. EFV is not active against HIV-2. The synergistic effect of TDF, FTC, and EFV were demonstrated in vitro to be the result of enhanced formation of "dead-end complexes" made up of HIV-1 strand-terminated DNA in the presence of all three drugs, which was superior when compared to two of the drugs in combination.[21]

## Efficacy

The Gilead Study 934 was the first to show the combination of TDF–FTC–EFV to be noninferior to the existing standard of care.[22] This prospective randomized open-label noninferiority trial compared 517 patients treated with the NRTI combination lamivudine (3TC)–zidovudine (ZDV) (Combivir®; GlaxoSmithKline, Research Triangle Park, NC) + EFV or TDF–FTC (Truvada®; Gilead Sciences) + EFV. The primary end point was time to loss of virologic response defined as HIV viral load $\leq 400$ copies/mL at 48 weeks. Of patients taking Truvada–EFV, 84% achieved virologic suppression compared with 73% in the Combivir–EFV group ($P = 0.002$), which met criteria for noninferiority and on secondary analysis was noted to be superior. In the intention-to-treat (ITT) analysis, an endpoint of HIV viral load was $\leq 50$ copies/mL, 77% of patients taking TDF–FTC–EFV and 68% of those taking 3TC–ZDV–EFV achieved virologic suppression ($P = 0.02$), which confirms the noninferiority of the regimen. The proportion of patients with grade 2–4 adverse events was similar in the two groups, however more patients in the 3TC–ZDV–EFV than in the TDF–FTC–EFV group discontinued their medication due to an adverse event (9% vs 4%), mostly due to anemia. At the 144-week analysis of the cohort, 64% of patients maintained viral suppression in the TDF–FTC–EFV arm compared to 56% of the ZDV–3TC–EFV ($P = 0.08$).[23] These results remained robust at 5 years of follow-up.[24]

Since then this combination has been the standard against which all other regimens have been compared. The fixed-dose combination Atripla and the individual components have been evaluated in a number of clinical trials in comparison to alternate agents including NNRTI (nevirapine, etravirine [ETR], rilpivirine [RPV]), ritonovir-boosted protease inhibitor (PI-r) (lopinavir–ritonavir [LPV–r], atazanavir–ritonavir [ATZ–r]) integrase inhibitors (raltegravir [RAL], elvitegravir), and CCR-5 inhibitors (maraviroc).[25–35] In the studies to date, largely of noninferiority design, and using the primary endpoints as defined by the studies, Atripla has not been beaten for efficacy by any other agent.

In addition to conclusions about noninferiority, these clinical trials have highlighted other findings worth mentioning. AIDS Clinical Trials Group (ACTG) study 5142

found EFV-based therapy not only noninferior, but superior to boosted protease inhibitor LPV–r-based therapy (viral load < 50 copies/mL at 48 weeks 89% vs 77%; $P = 0.003$).[31] The Mexican equivalent of ACTG 5142 also found EFV to be superior to LPV–r in a more advanced treatment-naïve population (see Table 1).[32] A subgroup analysis of ACTG study A5202 noted the TDF–3TC NRTI combination to have fewer virologic failures than abacavir (ABC)–3TC in patients with HIV-1 RNA viral load $\geq$ 100,000 copies/mL when combined with EFV or the boosted PI ATZ (7% failure rate at 48 weeks compared with 14%; hazard ratio [HR], 2.33; 95% confidence interval [CI]: 1.46 to 3.72; $P < 0.001$).[29] When comparing groups in a higher virologic strata (HIV-1 viral load $\geq$ 100,000 copies/mL), patients taking ABC-3TC combined with boosted-ATZ had higher rates of virologic failure than those taking ABC-3TC combined with EFV (HR, 1.68; 95% CI: 1.08 to 2.60; $P = 0.019$).[37] The Altair study found that a quadruple NRTI regimen (TDF–FTC–ZDV–ABC) was inferior to TDF–FTC–EFV, mostly due to therapy discontinuations from adverse events in the ITT analysis, although there was no difference of the latter to TDF–FTC–ATZ–r.[30]

The STARTMRK study was the first study comparing TDF–FTC–EFV to an integrase inhibitor-based regimen. 566 treatment-naïve patients were randomized to Truvada (TDF–FTC) plus either EFV or RAL.[35] Patients were given placebo pills in order to preserve blinding of the third agent as EFV was taken once daily, and RAL twice daily. At 48 weeks 86% of patients in the RAL arm and 82% of patients in the EFV arm remained virologically suppressed on the initial regimen, meeting the noninferiority criteria. These results remained robust at 156 weeks of treatment, at which time point superiority of RAL was demonstrated in addition to noninferiority.[36] Time to virologic response was shorter for the RAL group (>80% with suppressed viral load at 12 weeks vs 24 weeks for EFV), however the clinical significance of this result is uncertain as immune response was similar in both groups. In assessing the results of this study, it is important to note that the double-blind design required patients in both groups to take multiple pills to allow for placebo control. While preserving blinding, this would not allow for assessment of any advantage that a single-tablet regimen (STR) such as Atripla might have over a twice-daily regimen.

The multitablet regimen of TDF–FTC–EFV now coformulated as Atripla has been rigorously shown to be effective, in the short- and long-term, in demographically, and immunologically diverse populations.[38] It remains the preferred NNRTI-based regimen by the DHHS, European

**Table I** Randomized controlled clinical trials of efficacy of EFV–FTC–TDF in ARV-naïve subjects

| Study | cART regimen | Study design[∞] | Follow-up time (weeks) | Number of subjects | Baseline CD4+ T-cell count; mean (cells/mm³) | Baseline HIV-I RNA, median (log₁₀ copies/mL) | % of patients with HIV RNA ≤ 50 copies/mL at 48 weeks (ITT analysis) | CD4+ T-cell increase; mean (cells/mm³) |
|---|---|---|---|---|---|---|---|---|
| Gilead 934[22] | TDF-FTC-EFV | Open label | 48 | 244 | 233 | 5.0 | 77* | 190 |
| | ZDV-3TC-EFV | | 48 | 243 | 241 | 5.0 | 68* | 158 |
| ACTG 5142[31] | TDF-3TC-EFV+ | Open label | 96 | 250 | 195 | 4.8 | 62++ | 230++ |
| | TDF-3TC-LPV/r+ | | 96 | 253 | 190 | 4.8 | 50++ | 287++ |
| Mexican 5142[32] | ZDV-3TC-EFV | Open label | 48 | 95 | 64 | NR | 71§ | 234 |
| | ZDV-3TC-LPV/r | | 48 | 94 | 52 | NR | 53§ | 239 |
| ACTG | TDF-FTC-EFV | Open label | 96 | 464 | 234 | 4.7 | 90#* | NR |
| A5202[29] | TDF-FTC-ZDV/r | | 96 | 465 | 224 | 4.7 | 84#* | NR |
| | ABC-3TC-EFV | | 96 | 465 | 225 | 4.7 | 87#* | NR |
| | ABC-3TC-ATZ/r | | 96 | 464 | 236 | 4.6 | 78#* | NR |
| STARTMRK[35] | TDF-FTC-EFV | Double blind | 156 | 281 | 217 | 5.0 | 82#* | 163 |
| | TDF-FTC-RAL | Double blind | 156 | 282 | 219 | 5.0 | 86#* | 189 |
| ECHO[28] | TDF-FTC-EFV | Double blind | 96 | 346 | 257 | 5.0 | 83$* | 182 |
| | TDF-FTC-RPV | Double blind | 96 | 344 | 240 | 5.0 | 83$* | 196 |

**Notes:** [∞]All studies were of prospective, randomized, noninferior design; [∞]noninferior design; *noninferior; †patients took 3TC–TDF or AZT or SDV; ++analysis done at 96 weeks; #per protocol analysis; §TLOVR, time to loss of virologic response (composite end-point where failure means virologic failure, death, loss to follow-up or change of drug for any reason).[142]
**Abbreviations:** EFV, efavirenz; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine; 3TC, lamivudine; SDV, stavudine; LPV–r, lopinavir–ritonavir; ABC, abacavir; ATZ–r, atazanavir–ritonavir; RAL, raltegravir; RPV, rilpivrine; NR, not reported.

AIDS Clinical Society, and International AIDS Society USA guidelines.[1–3]

## Adverse effects and prescribing considerations

Atripla generally tends to be well tolerated. The most frequently reported side effect of EFV is central nervous system (CNS) disturbances manifesting as dizziness, sleep disturbance, vivid dreams, poor concentration, or change in mood which occur in a majority of patients. These symptoms which are often mild and resolve with 2–4 weeks, can be helped with sleeping aids or benzodiazepines, and rarely lead to drug discontinuation.[4] Symptoms can persist in some patients and result in long-term sleep disturbance, mood change, lethargy, and cognitive dysfunction.[39,40] The side effects may resolve when EFV is switched to another agent. More concerning psychiatric complications such as severe depression and suicidal ideation may rarely occur, particularly in patients with pre-existing psychiatric disorders and substance abuse problems.[4,41,42] Genetic polymorphisms in CYP2B6, found more frequently in African-Americans, can lead to higher EFV concentrations and may explain higher rates of neurologic side effects.[43] In some studies, women may be more likely to discontinue EFV due to CNS toxicity, perhaps related to drug levels.[44]

EFV can be associated with maculopapular rash in 23% of patients. Though usually self-limited, and not associated with systemic illness or mucosal ulceration, it can rarely progress to Stevens-Johnson syndrome which would preclude the further use of EFV or any other NNRTI.[45,46] Lipid disturbances, particularly increased low-density lipoprotein and total cholesterol that frequently complicate the use of PI are also seen with EFV.[31,32] Lipoatrophy can be seen with both PIs and EFV. Although more likely related to the backbone NRTI, more lipoatropy was seen with EFV than LPV–r in ACTG 5142,[31] although similar rates were seen when compared to ritonavir-boosted ATZ in study ACTG 5202.[47]

EFV was initially listed as an FDA pregnancy category "C" drug due to birth defects in animal models.[48] This was changed to category "D" after a number of isolated case reports of human neural tube defects following first-trimester exposure to EFV in humans.[49,50] The issue remains controversial and although some studies have reported increased risk, a recent meta-analysis questions the teratogenicity concern.[51] When options exist, experts and guidelines still recommend alternative agents in the first trimester.[1–3] EFV inhibits hepatic isoenzyme CYP3A4, and caution must be used when coadministering drugs metabolized by this pathway.[4] CYP2B6 is the hepatic enzyme primarily implicated in EFV metabolism and is induced by rifampin. In patients with coinfected with tuberculosis who are taking rifampin and a ≥60 kg dose adjustment of EFV may be required. A single 200 mg tablet of EFV can be added to Atripla to make the total dose 800 mg. EFV can induce metabolism of rifabutin via the CYP3A4 pathway, and rifabutin doses should be increased to 450 mg daily.[1,52,53]

TDF-associated nephrotoxicity is primarily a consequence of proximal renal tubular dysfunction, and can lead to Fanconi's syndrome, nonoliguric or oliguric renal failure, and rarely acute kidney injury leading to end-stage renal disease.[54–56] Renal function may normalize after discontinuing TDF. Patients at increased risk are those with low body weight, advanced age, pre-existing renal disease, higher serum creatinine levels before starting tenofovir, advanced HIV infection and concomitant use of other renal toxic agents, and possibly coadministration of PI–r.[57–59] Multiple clinical trials largely in well, naïve populations, however have not found a notable decrease in renal function related to use of TDF, perhaps due to strict inclusion criteria which would limit patients with elevated risk.[57,60–63] In patients with decreased glomerular filtration rate (GFR), Atripla cannot be used as TDF-dose adjustment is required. In those with GFR $< 90$ mL/min/1.73 m[2], or other risk factors for renal toxicity consideration should be made for biannual monitoring of renal function, serum phosphorus, proteinuria and glycosuria.[1,64]

Proximal tubule dysfunction related to TDF can lead to phosphate wasting, osteomalacia, and decreased bone mass.[65–67] In the ASSERT study, patients taking TDF/FTC were found to have increased rates of bone turnover as measured by surrogate markers, and bone mineral density loss compared to those taking ABC–3TC, particularly in the spine and hip, and in the initial period after the introduction of antiretrovirals.[58,69] Although the long-term consequence of this remains controversial, a recent retrospective cohort study found a small increased fracture risk in patients taking TDF (odds ratio [OR], 1.08; 95% CI: 1.02–1.15; $P < 0.001$).[70]

FTC is generally well tolerated in cART, and side effects most commonly reported are headache (13%), diarrhea (23%), nausea (18%), and rash (17%).[71] Approximately 1% of patients discontinued FTC due to side-effects. Hyperpigmentation of the skin of the palms and soles is described with FTC use in 2%–6% of patients, but is not typically perceived of as a significant event, and has not led to treatment discontinuation.[71] TDF and FTC are active against hepatitis B infection, and effective in treating

coinfected patients. Clinicians must be aware that serious viral rebound and hepatitis flares can occur if the TDF–FTC are discontinued abruptly in coinfected patients.[72–74]

## Adherence, patient preferences, QoL, and regimen durability with Atripla

Medication adherence is well known to be critical to success of all ART regimens.[1–3] Adherence is required for optimal suppression of viral replication and immune reconstitution.[75–76] In patients with low CD4+ counts at onset of treatment, poor adherence can be a predictor of death.[75] For those who are stable on cART, poor adherence leads to virologic failure and the development of drug resistance.[77] Many factors may contribute to suboptimal adherence including but not limited to cognitive dysfunction, substance abuse, concerns regarding confidentiality and disclosure, psychiatric disorders, medication side effects, access, and the complexity of medication regimen or "pill burden."[78] When asked, patients reported total pills per day, and dosing frequency as the most important factors affecting their own ability or perception of their ability to adhere to cART regimen.[79]

Decreasing pill burden and frequency of dosing has been shown to improve medication adherence in many disease disorders as well as in HIV, and that even small reductions in pill count can help.[80,81] A meta-analysis of eleven clinical trials found that significantly better adherence (+2.9%; 95% CI: 1.0%–4.8%; $P < 0.003$) was seen in once-daily dosing cART regimens compared to twice-daily regimens.[82] Switching from two separate NRTIs to combination pills has also shown to improve adherence and patient satisfaction.[83,84] Additionally, patients on NNRTI-based regimens have been shown in the past to have better adherence than those on PI-based regimens, likely at least in part due to the relatively low pill count and simplicity of NNRTI combinations,[85] though this has never been confirmed in a randomized trial. The importance of decreased regimen complexity and pill burden may be most important in those with significant social barriers to care. Bangsberg et al in a recent prospective observational study of 118 homeless and marginally housed individuals compared to historical controls found that the use of a STR– of EFV–FTC–TDF resulted in significantly higher adherence.[86] Periodic assessments of adherence via pill counts over a 6-month period showed a mean adherence of 86% of the STR (SD ± 18%), compared to 75% (SD ± 21%; $P = 0.006$) for PI-based regimens, and 68% (SD ± 26%; $P = 0.02$) for multitablet NNRTI-based regimens. The proportion of patients achieving adherence ≥ 90% was 58% for the STR, and just 35% for all other regimens ($P = 0.02$). Not surprisingly viral suppression (HIV RNA ≤ 50 copies/mL) was greater in the EFV–FTC–TDF STR group compared to the non-STR group (46%; $P = 0.02$).[86]

A retrospective database study of 7,023 commercially insured patients in the US also found patients taking single-tablet HIV regimen were more likely to achieve high levels of adherence (≥95%) than those taking two or more pills per day ($P = 0.001$).[87] Over the 31-month study period the patients in the single-table group were also found to less likely to be hospitalized for any reason (OR = 0.76; $P = 0.003$). This association between adherence and risk of hospitalization has been noted previously.[87,88] The ADONE study (Adherence to ONE pill) also studied adherence and patient reported QoL in 212 virologically suppressed patients who had their baseline regimen changed from individual components of either EFV+TDF+FTC or 3TC+TDF+EFV to the STR of EFV–FTC–TDF and were followed for 6 months. In a stable population, with already high adherence rates, those patients switching to a STR reported increased mean adherence from 93.8% to 96.2% ($P < 0.01$) at 1 month of follow-up. The benefit remained statistically signficant at 6 months.[89]

Optimal approaches to improving medication adherence in patients with HIV include: building strong physician–patient relationships, education on the risk of resistance, explaining and monitoring for medication side effects and treating underlying psychological illnesses.[90] Decreased cART regimen complexity and pill burden is one strategy to improve adherence, and is shown to be effective with the choice of a single-dose tablet combination of EFV–TDF–FTC.

## Patient preference and QoL

A study from Dejesus and colleagues in 2009 aimed to evaluate the impact of switching patients on either a NNRTI- or PI-based regimen to a STR of EFV–TDF–FTC.[91] Three hundred patients were randomized to either continue their current regimen, or to switch to a single-dose tablet of EFV–TDF–FTC. QoL was assessed using the Medical Outcomes Study 36-item Short Form survey (SF-36) questionnaire version 2,[92] a validated QoL-assessment tool. At 48 weeks after switch, the study group found a small, but significant increase in the physical QoL scores amongst the patient taking the STR at final assessment, but overall SF-36 scores, and QoL in the mental, and health domains were unchanged. More favorable outcomes were observed regarding patient preference. At 48 weeks, 85% of patients said that EFV–TDF–FTC was "much better" than their previous regimen, and 97% of patients found EFV–TDF–FTC "very easy to take" compared

with 81% of patients taking their previous medication regimen ($P < 0.001$).

In the ADONE study discussed previously, QoL and patient preferences were evaluated in patients switching to fixed-dose EFV–TDF–FTC. QoL was evaluated using a modifed SF-36 form. Patient preference was monitored by asking patients to quantify questions related to tolerability, convenience, simplicity, and potency. Patients reported a statistically significant improvement in all preference-based questions, particularly regarding convenience and simplicity of the regimen. While QoL was improved in many areas, there was a statistically significant decrease in time with negative feelings (nervous or worn out) from 40.3% to 31.5% ($P < 0.0001$). There was a nonstatistically significant trend to improvement in other QoL measures such as limitations to everyday social and work activities posed by illness, and presence of positive feelings improved, but, the overall QoL score did show an improvement in the fixed-dose group (95% CI score 68.7 increased to 72.7, $P = 0.042$).[89]

It has been difficult to clearly demonstrate scientifically that the fixed-dose combinations can improve clinical outcomes. Hodder et al showed that patient preference is higher among patients switching to fixed-dose EFV–TDF–FTC from other cART regimens though there was not an improvement in overall QoL.[13] This open-label study randomized 300 virologically suppressed patients on a PI- or NNRTI-based regimen to either stay on the same regimen, or change to fixed-dose EFV–TDF–FTC. Of the 203 patients that were switched, 47% were previously on an NNRTI, and 53% on a PI-based therapy for at least 3 months. QoL was assessed using the SF-36 questionnaire version 2.[92] At baseline, QoL scores were similar between the treatment groups, and changes in QoL scores in the switch arm were small and did not meet criteria for statistical significance. Notably, 91% of patients receiving the fixed-dose medication reported the regimen was either "much better" or "slightly better" from a preference standpoint at 48 weeks.

## Regimen durability

Regimen persistence is defined as "the duration between the initiation and discontinuation of a specified antiretroviral regimen as agreed upon by the patient and the health care provider."[93] Regimen durability refers to the length of time a patient stays on a particular cART regimen whether switching is due to virologic failure, side effects, or other reasons.[14] Durability of cART regimens is important as second-line regimens can be associated with additional medication side effects, higher cost, and suboptimal efficacy if resistance had

emerged. Poor patient persistence is associated with virologic failure, accumulation of drug resistance, and complete discontinuation of medication. In a recent review a high number of pills, significant side-effects, and frequent dosing schedules were cited as reasons for early medication discontinuation.[93]

A study from the University of Alabama retrospectively compared cART regimen durability based on number and frequency of pill administration in 542 treatment-naïve patients starting cART between January 2000 and July 2007.[14] When compared with earlier regimens, the advent of fixed-dosed regimens in 2004 such as Truvada, Combivir, and Kivexa®/Epzicom® (ViiV Healthcare, Research Triangle Park, NC) had a major impact on regimen durabilty.[14] Median durability of regimens with three tablets or less was 1281 days (95% CI: 961–1724 days), compared with 766 days (95% CI: 468–1263 days) for 4–5 pill regimens, and 340 days for regimens with ≥6 pills. Once daily regimens were significantly more durable than twice-daily regimens (1252 vs 712 days).[14]

Another retrospective study from Spain compared patients starting EFV–TDF–FTC or TDF–FTC + EFV and found that those on the two-pill regimen had a lower probability of altering their treatment at 12 months.[94] This result was not statistically significant ($P = 0.14$), possibly related to the small sample size, but further study will likely support the durability of a once-daily, single-tablet cART regimen.

From these studies it is easy to infer that patients prefer a single-tablet once daily regimen to a more complex one. This may facilitate good physician–patient relationships, allow patients to feel less "medicated", and have a long-term impact on adherence and regimen durability. QoL after changing to fixed-dose EFV–TDF–FTC shows improvement in some studies, and is likely a multifactorial issue, one in which regimen-dosing simplicity can only help.

## Resistance

When taken consistently, cART results in excellent viral suppression which can slow or prevent the development of HIV drug resistance, prevent viral rebound, and extend the durability of treatment regimens.[10,95–100] Transmitted drug resistance (TDR) remains an important issue to consider before choosing any first-line cART. Recent large population-based studies in the United States, Africa, and Europe have found TDR rates in the range of 6%–16%, with higher levels of resistance in certain urban populations, particularly those who engage in high-risk sex and intravenous drug users (Table 2).[101–110] In a study of 1277 newly infected patients with HIV-1 in South Carolina, 184 (14%) had TDR. Of these

**Table 2** Rates of possible transmitted drug resistance to components of Atripla by region

| Region | Years | Number of patients | Median age | % Male | % MSM | % IVDU | Median CD4 ct (cells/mm³) | Median HIV-1 RNA viral load (log copies/mL) | Any RAM % | NNRTI RAM % | NRTI RAM % | Dual or triple class RAM % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Switzerland[106] | 1996–2005 | 822 | NR | 77 | 42 | 20 | 536 | 5.0 | 7.9 | 2.0 | 6.0 | 2.0 |
| EuroSIDA[§,107] | 1996–2004 | 525 | 37 | 75 | 50 | 21 | 251 | 4.9 | 11.4 | 5.0 | 9.3 | 1.7 |
| San Francisco[108] | 2002–2009 | 372 | 32 | 95 | 96 | 9 | 520 | 4.8 | 16.0 | 8.0* | 11.0* | NR |
| Spain[109] | 2004–2008 | 683 | 34 | 86 | 61 | 10 | 395 | 4.5 | 8.5 | 4.0 | 4.4 | 1.8 |
| China[110] | 2004–2005 | 676 | 38 | 68 | NR | 17 | 280 | 4.6 | 3.8 | 2.1 | 1.6 | 0.8 |
| Mexico[111] | 2005–2010 | 1655 | 33 | 80 | NR | NR | 228 | 4.9 | 7.4 | 2.5 | 4.2 | 0.9 |
| USA[¶,112] | 2006 | 2030 | NR | 75 | 47 | 4 | NR | NR | 14.6 | 7.8 | 5.6 | 2.6 |
| South Carolina[113] | 2005–2009 | 1277 | 35 | 72 | 43 | 3.8 | 415 | 4.3 | 14.4 | 10 | 4 | 1.3 |
| Sub-Saharan Africa[#,114] | 2007–2009 | 2436 | 38 | 43 | NR | NR | 133 | 4.9 | 5.6+ | 3.3 | 2.5 | 1.2 |

**Notes:** *2009 value, average not reported; #Zambia, South Africa, Uganda, Kenya, Zimbabwe, Nigeria; +prevalence much higher in Uganda (11.6%) vs all other sites (3.5%); §93 centers in Europe, Israel, and Argentina; ¶data from Variant, Atypical and Resistant HIV Surveillance System of 10 USA states.
**Abbreviations:** RAM, resistance-associated mutation; MSM, men who have sex with men; IVDU, intravenous drug users; NRTI, nucleoside reverse-transcriptase inhibitors; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NR, not reported.

54 (4%) had an NRTI mutation, 37 (3%) had a PI mutation, and 126 (10%) had an NNRTI mutation. Nineteen patients (1.4%) had dual class-associated mutations and seven (0.5%) had triple-class associated mutations. Patients with pre-existing drug resistance starting cART have been found to be at higher risk for virologic failure.[86] A recent observational study showed patients who did not have genotypic testing prior to treatment initiation were also at a higher risk of death.[111] Current DHHS guidelines recommend obtaining HIV-1 genotypes to identify common TDRs before initiating cART in treatment-naïve patients.[1]

In newly infected patients, the ability to identify TDR decreases with time as drug resistant mutants are overgrown by or revert to wild type strains.[112,113] Minority HIV-1 sub-types can harbor resistance, which is not detected by current widely used genotypic analysis assays.[114,115] Minority variants are found most frequently in treatment-experienced patients, but can also be seen in treatment-naïve patients as a result of TDR. These undetected resistant associated mutations may cause suboptimal response to ART and lead to rapid emergence of HIV drug resistance, and can be implicated in early treatment failures.[116–120]

Unequal exposure to antiretrovirals and treatment inter-ruptions are thought to underlie the development of resistance in some patients.[121–125] Different rates of adherence to medica-tions within a regimen (discordant adherence) combined with varied pharmacokinetics of the agents can lead to viral rep-lication, and subsequent exposure to sub-optimal treatment regimens.[77,98,126,127] Fixed-dose regimens such as Atripla may promote more complete adherence in a "take one, take all" fashion which would limit unequal viral exposure to cART components. Whether this would lead to reduced emergence of resistance in patients taking fixed-dose combinations is unknown, but is an area where more study is needed.

For the first-generation NNRTIs, a single mutation can confer drug resistance, and can be described to have a low genetic barrier, as compared with PI/r which requires many resistance-associated mutations (RAMs) in order to develop high-level resistance.[125,128–132] Consequently, periods of inter-mittent or incomplete adherence can put the patient at risk for resistance even if the level of viral replication is low. The most frequently identified NNRTI-resistant mutation in patients failing Atripla-based cART therapy is K103N (Table 3),[130,131] which confers resistance to EFV and also to nevirapine, but not second-generation NNRTIs such as ETR (Intelence®; Janssen Therapeutics, Titusville, NJ) and RPV (Edurant®, Janssen Therapeutics),[125,133,134] Although the absolute number of virologic failures to EFV-based regimens in clinical trials

**Table 3** Emergence of resistance-associated mutations in patients failing Atripla

| Study | 934[22] | ACTG 5142[31] | Mexican ACTG 5142[32] | ACTG A5202[29] | STARTMRK[35] | ECHO[28] |
|---|---|---|---|---|---|---|
| Follow-up time (weeks) | 144 | 48 | 48 | 138* | 156 | 48 |
| Number of subjects | 244 | 250 | 95 | 464 | 282 | 346 |
| Virologic failures n (%) | 19 (8) | 60 (24) | 7 (7) | 57 (12) | 54 (19) | 19 (6) |
| RAMs n (%) | 13 (5) | 22 (9) | 6 (6) | 27 (6) | 16 (6) | 13 (4) |
| NNRTI n (% of RAMs) | 13 (100) | 20 (91) | 3 (43) | 27 (100) | 7 (44) | 8 (62) |
| K103N n (% of RAMs) | 8 (62) | 11 (50) | 2 (29) | 19 (4) | 7 (44) | 7 (54) |
| NRTI n (% of RAMs) | 2 (15) | 14 (64) | 1 (14) | 11 (41) | 9 (56) | 4 (31) |
| M184V/I n (% of RAMs) | 2 (15) | 8 (36) | 0 (0) | 5 (19) | 2 (13) | 4 (31) |
| K65R n (% of RAMs) | 0 (0) | 3 (14) | 1 (14) | 4 (21) | 0 (0) | 0 (0) |
| TAMs+ n (% of RAMs) | 0 (0) | 2 (9) | 0 (0) | 2 (7) | 7 (27) | 0 (0) |
| Dual class (NRTI–NNRTI) n (% of RAMs) | 2 (15) | 12 (55) | 1 (14) | 11 (41) | 7 (44) | 4 (31) |

**Notes:** *Median; +thymidine analogue mutation.
**Abbreviations:** RAM, resistance-associated mutation; NRTI, nucleoside reverse-transcriptase inhibitors; NNRTI, non-nucleoside reverse-transcriptase inhibitor.

is low, about half of those failing therapy do show evidence of NNRTI-related mutations.[22,25,28,29,31,32] In addition to K103N, Y188L, and G190S/A mutations can lead to high-level EFV resistance.[125,130,132] Other mutations that decrease virologic response to EFV are: L100I, K101P, V106M, V108I, Y181C/I, and P225H.[125,130,132] The longer the patient continues on a failing regimen, the greater the numbers of mutations that develop, which can then also compromise the second-generation NNRTIs.[132]

TDF and 3TC have reduced efficacy when K65R or thymidine analogue-associated mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) are present.[125] M184V/I, a mutation which is associated with resistance to 3TC also confers resistance to FTC, and is an early mutation that emerges with virologic failure on either agent.[125,112] K65R or K70E which can emerge on treatment with TDF can cause decreased response to tenofovir, ABC, and 3TC.[125,128,135]

If virologic failure is observed in patients taking TDF–FTC–EFV repeat genotypic testing should be done as soon as possible as drug resistance can develop even with low level viremia.[136] If K103N is detected early after virologic failure second generation NNRTIs might be useful before further resistance develops.[131–135] Boosted PIs and integrase inhibitors are also reasonable salvage options should EFV resistance be detected. Regardless of antiretroviral choice, three drugs to which the virus is susceptible should be initiated.[1]

## New STRs

Complera (Gilead Sciences), a STR comprised of TDF, FTC, and RPV, a second-generation NNRTI was recently approved by the FDA for treatment-naïve patients.[137] Two Phase III clinical trials (ECHO and THRIVE) have shown the Complera combination to be noninferior to Atripla in treatment-naïve patients with HIV-1 infection.[27,28] Patients taking RPV reported fewer neurological side effects than those taking EFV (17% vs 38%) had a better lipid profile on therapy and were less likely to discontinue the regimen due to treatment side effects (3% vs 8%). In subgroup analysis, patients in the RPV arm with a baseline viral load $\geq$ 100,000 copies/mL had a significantly higher rate of virologic failure than in the EFV arm at 48 weeks (15% vs 6%), and viral failure was associated with an increased rate of drug resistance.[138] The mutations most commonly observed in patients failing RPV-based therapy were E138K and K103I. The isolates from these patients were frequently phenotypically resistant to other NNRTIs including nevirapine (45%), EFV (87%), and ETR (90%). M184V/I were also significantly more frequent in patients failing RPV.[138] Complera is an alternative to patients in whom Atripla is contraindicated because of CNS issues, or may be used as switch therapy in those with intolerance to EFV. Caution should be used in patients with baseline viral load $\geq$ 100,000 copies/mL.

The Quad tablet (Gilead Sciences), a combination of TDF, FTC, elvitegravir (GS-9137; Gilead Sciences),

a second-generation integrase inhibitor, and a novel boosting agent cobicistat (GS-9350; Gilead Sciences) has been submitted to the FDA for approval based on a recent Phase III clinical trial of 700 treatment-naïve patients demonstrating its noninferiority to Atripla, and similar rates of adverse events and drug discontinuations.[33] The Quad tablet was also found to be noninferior to TDF–FTC and ATZ–r.[139] Whether or not it will have advantages in terms of long-term efficacy, tolerability, or cost effectiveness is unknown.

The SPRING-1 study described a 96 week Phase IIb dose-finding comparing a novel integrase inhibitor dolutegravir (S/GSK1349572; ViiV Healthcare, Brentford, UK) or EFV combined with TDF and FTC or ABC–3TC.[140] Again, noninferiority was demonstrated, but further data on efficacy and tolerability will be presented upon the completion of the ongoing Phase III clinical trials. Dolutegravir is also being developed as a fixed-dose tablet combined with ABC and 3TC.[141]

## Conclusion

Atripla is the first, but no longer the only, fixed-dose combination for the treatment of HIV-1 infection in adults. It has proven highly efficacious when compared against other available regimens and classes and remains a DHHS "preferred" regimen for treatment-naïve patients starting cART. Patients prefer the simplicity of a once-daily treatment regimen, and when switched to Atripla report an improved QoL. Atripla has excellent treatment durability, which may benefit all patients, particularly those groups with barriers to taking medication frequently. Atripla is generally well tolerated, though caution should be used prescribing Atripla to patients with previous psychiatric illness, renal insufficiency or women considering pregnancy. If patients have TDR to any of Atripla's components another regimen should be selected. Although the emergence of resistance has remained low, likely because of the tolerability and long half-life, adherence is crucial given the low genetic barrier. The most frequent mutations that are detected among patients failing Atripla were K103N and M184V/I. In order to preserve treatment options, resistance testing should occur as soon as possible in the event of viral failure. Atripla has extensive clinical trial and provider experience; however, it will soon come under challenge. Complera, a second STR for HIV-1 infection is now approved for use, and a number of other fixed-dose regimens are on the horizon. More data are needed to recommend these regimens as first-line therapy, but it is clear that patients with HIV-1 infection will soon have a great deal of convenient and effective single-tablet, once-daily treatment choices. In this way, the appropriate agent can be tailored to the patient. It is an exciting time for both patients and health care providers.

## Disclosure

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