The transformation of HIV therapy: One pill once a day

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Abstract
A co-formulated, one pill once a day antiretroviral regimen (single-tablet regimen), containing efavirenz, emtricitabine, and tenofovir disoproxyl fumarate (Atripla), revolutionized the antiretroviral therapy landscape. Single-tablet regimens provide not only dosing convenience but help optimize adherence and persistence with antiretroviral therapy to achieve durably suppressed viremia with both individual and societal benefits. Given the many excellent options available now, single-tablet regimens are the preferred choice for initiating antiretroviral therapy in almost all patients with rare exceptions for drug interactions and pregnancy, and for simplification of more complex antiretroviral therapy to a single-tablet regimen. In this special commemorative article, we celebrate this astounding advancement in antiretroviral therapy, championed by John C. Martin while CEO of Gilead Sciences, and its transformative impact on HIV care nationally and globally.

Keywords
HIV, single-tablet regimen, co-formulated, antiretroviral therapy

Azidothymidine (AZT; zidovudine) was initially developed in 1964 as a potential cancer therapy and shelved soon after when found to be ineffective. It was resurrected in the 1980’s when scientists from the National Cancer Institute and Burroughs Wellcome pharmaceutical company identified it as a potent inhibitor of HIV-1, which in 1983, had been discovered to be the cause of acquired immunodeficiency syndrome (AIDS). In March 1987, AZT became the first U.S. Food and Drug Administration (FDA) approved drug for treatment of AIDS. Initial approval was limited to AIDS and symptomatic cases of AIDS-related complex and later expanded to pre-AIDS and non-advanced cases. It was recognized early during clinical trials that zidovudine prolonged short-term survival but drug resistance developed rapidly [1], which led to clinical trials of two-drug combination therapy. Results from the initial two-drug therapy trials (ACTG 175, CPCRA 007 and Delta) showed modest or no significant benefit over zidovudine alone. The combination of zidovudine and lamivudine briefly became the standard of care, achieving sustained increases in CD4+ T-cell counts for more than 1 year in both treatment naïve and zidovudine-experienced patients [2,3]. The discovery of potent HIV-1 protease inhibitors (PIs) including indinavir led to studies of three-drug regimens including indinavir, zidovudine, and lamivudine, which achieved, for the first time, sustained viral suppression (Merck 035) [4] and markedly reduced progression to AIDS and death compared with zidovudine and lamivudine (ACTG 320) [5]. This new era of highly active antiretroviral therapy led to a paradigm shift to three-drug regimens and was lifesaving; however, daily dosing was complex and burdensome side effects made long-term adherence difficult. To decrease pill burden, nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) were co-formulated as fixed drug combinations (FDC) with...
Combivir, a combination of AZT and lamivudine (3TC), gaining FDA approval on 1 September 1997, as the first one-pill combination for HIV/AIDS infection followed by Truvada (emtricitabine 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg) and Epzicom (abacavir sulfate 600 mg and lamivudine 300 mg) on 2 August 2004. Trizivir (co-formulated abacavir/lamivudine/zidovudine) one tablet twice a day was briefly considered to be the complete FDC antiretroviral regimen. In a multi-centered randomized study of antiretroviral-naive HIV-1-infected adults, the triple-nucleoside regimen of abacavir plus zidovudine/lamivudine was equivalent to the regimen of indinavir plus zidovudine/lamivudine in achieving plasma HIV-1 RNA level of less than 400 copies/ml at 48 weeks [6].

Trizivir received FDA approval for the treatment of HIV-1 infection either alone or in combination with other anti-retroviral regimens in November 2000. A subsequent study (A5095) compared abacavir/lamivudine/zidovudine, zidovudine/lamivudine plus efavirenz, and abacavir/lamivudine/zidovudine plus efavirenz for initial treatment of HIV-1 infection. The triple-nucleoside combination of Trizivir was virologically inferior to a regimen containing efavirenz and two or three nucleosides [7], which removed it from being recommended as a preferred therapy in HIV-1 treatment guidelines. The combination of TDF and emtricitabine (FTC) plus efavirenz (EFV) was demonstrated to be virologically superior and better tolerated compared to a FDC of zidovudine and lamivudine plus EFV [8]. Accordingly, TDF or abacavir (ABC) in combination with 3TC or FTC became the preferred NRTI backbone for treatment-naive patients. EFV received its initial approval in the United States in 1998 with 200 mg capsule formulation for a therapeutic daily dose of 600 mg and in combination with two NRTIs, requiring 5–6 pills once or twice a day. The subsequent formulation of a 600 mg EFV tablet led to a widely prescribed two pill once a day regimen (EFV + FDC TDF/FTC), especially for those newly initiating HIV-1 therapy. By 2004, there were more than 20 unique antiretroviral drugs approved in the United States with only a few approved for use as FDC products and none as co-packaged products or single-tablet regimens (STRs), leading the FDA to draft guidance for industry to encourage development of co-packaged products. On 20 December 2004, Gilead Sciences and Bristol–Myers Squibb announced the establishment of a U.S. joint venture to develop and commercialize a single-tablet regimen. The product Atripla combined Sustiva (EFV), manufactured by Bristol–Myers Squibb, and Truvada (TDF/FTC), manufactured by Gilead Sciences, gaining FDA approval on 12 July 2006 as the first once a day single-tablet regimen (STR) for the treatment of HIV-1 infection in adults.

Development of Atripla occurred through an unprecedented collaboration between Bristol-Myers Squibb and Gilead Sciences and was rightfully hailed as a landmark achievement. Gilead Sciences, through John Martin’s leadership and vision, continued to be at the very forefront of the STR innovation, with Complera (emtricitabine/ritonavir/TDF) in August 2011, followed by Stribild (elvitegravir/cobicistat/TDF/emtricitabine) in August 2012. In 2014, Triumeq (abacavir/dolutegravir/lamivudine), developed by ViiV healthcare, became the fourth STR for the treatment of HIV and in July 2018, the first and only PI-based STR Symtuza (daranavir/cobicistat/tenofovir alafenamide/emtricitabine) received FDA approval. As of September 2021, there are 13 co-formulated STR available in United States (Table 1) for HIV-1 treatment including one STR Juluca approved only for maintenance regimen for those with suppressed HIV-1 viremia.

Advantages of STRs

Effect of STRs on adherence and persistence with regimen

STRs decrease pill burden, reduce regimen complexity and improve adherence. In a meta-analysis of 11 randomized controlled trials with 3029 participants, the observed medication-taking rate was improved with once/day regimens over twice/day or 3 times/day regimens (odds ratio [OR] 2.9, 95% confidence interval [CI] 1.0–4.8, P < 0.003) [9]. In a study of commercially insured patients receiving antiretroviral therapy (ART) between 2006 and 2008, those receiving a single pill per day were significantly more likely to reach a 95% adherence threshold versus patients receiving three or more pills per day (odds ratio [OR] = 1.59; P < 0.001) [10]. The Women’s Interagency HIV Study, a longitudinal study of HIV-1 infection in U.S. women, examined semiannual trends in single-tablet regimen use and ART adherence during 2006–2013 [11]. A total of 15,523 person-visits, representing 1727 women (53% black, 29% Hispanic, 25% intravenous drug use, median age 47), were examined. Use of STR among ART users increased from 7% in 2006 to 27% in 2013; adherence increased from 78% to 85% during the same period (P < 0.001). STR use was significantly associated with increased adherence (adjusted RR 1.05, 95% CI 1.03–1.08) and virologic suppression (RR 1.06, 95% CI 1.01–1.11). A retrospective analysis of longitudinal pharmacy claims among U.S. patients initiating ART between 1 January 2016 and 31 May 2016 found that STR patients were more than 2 times likely to be adherent over 12 months than patients on multi-tablet regimens (MTRs) (24.9% vs 11.7%, respectively). Persistence with ART was also greater with STRs, with patients on MTRs being 61% more likely to discontinue therapy [12].

Effect of STRs on virologic suppression

It was recognized early during combination ART that the number of pills in a regimen was negatively associated with
plasma HIV-1 RNA ≤50 copies/ml at week 48 (P = 0.0085) [13]. This negative association was found in a systematic overview including data from 23 clinical trials involving 31 independent treatment groups, 19 unique antiretroviral regimens, and 3257 enrolled patients from clinical trials involving triple combination therapy with dual NRTI and a PI, a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a third NRTI. An updated meta-analysis in 2006 by the same investigators found pill count not to be a consistent predictor of virological suppression, which correlated with more effective NNRTI or PI-containing regimens, indicating that regimen potency is also key for efficacy [14]. In the era of once-daily regimens, a meta-analysis of 19 randomized controlled trials including 6312 adult patients, higher pill burden was associated with both lower adherence rates (P = 0.004) and worse virological suppression (P < 0.0001) in both once-daily and twice-daily subgroups [15]. Once-versus-twice-daily regimen improved adherence but not virological suppression. Both adherence and viral load suppression declined over time, but adherence decreased less with once-daily dosing than with twice-daily dosing. The Multicenter AIDS Cohort (MAC) observed an increase in STR use from 20% in 2008 to 51% in 2017 [16]. The percentage of visits with HIV-1 RNA below 50 copies/ml increased slightly from 84% in 2008 to 89% in 2017.

**Effect of STR on hospitalization risk**

Electronic health records reviewed from the Veterans Healthcare Administration demonstrated that U.S. veterans taking STR had a lower risk of hospitalization (HR: 0.71, 95% CI 0.59–0.86, P = NS) and extended time to hospitalization (median: 1508 vs 1032 days, P = 0.0042) [17]. Commercially insured patients on STR similarly were 24% less likely to have a hospitalization compared to multi-pill regimen (OR = 0.76; P = 0.003) [10].

| Trade name | ARV drugs in regimen | Wholesale acquisition monthly cost | Average wholesale monthly price |
|------------|----------------------|----------------------------------|-------------------------------|
| NNRTI plus two NRTI | | | |
| Atripla (EFV/TDF/FTC) | Efavirenz 600 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg | $2995 | $3594 |
| Generic | | | |
| Complera (RPV/TDF/FTC) | Rilpivirine 25 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg | $3089 | $3706 |
| Delstrigo (DOR/TDF/3TC) | Doravirine 100 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg | $2315 | $2778 |
| Odefsey (RPV/TAI/FTC) | Rilpivirine 25 mg/tenofovir alafenamide 25 mg/emtricitabine 200 mg | $3089 | $3706 |
| Symfi (EFV/TDF/3TC) | Efavirenz 600 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg | $1634 | $1961 |
| Symfi Lo (EFV/TDF/3TC) | Efavirenz 400 mg/tenofovir disoproxil fumarate 300 mg/lamivudine 300 mg | $1634 | $1961 |
| PI plus two NRTI | | | |
| Symtuza (DRV/c/TAF/FTC) | Darunavir 800 mg/cobicistat 150 mg/tenofovir alafenamide 10 mg/emtricitabine 200 mg | $4065 | $4878 |
| INSTI plus two NRTI | | | |
| Biktarvy (BIC/TAF/FTC) | Bictegravir 50 mg/tenofovir alafenamide 25 mg/emtricitabine 200 mg | $3394 | $4073 |
| Genvoya (EVG/c/TAF/FTC) | Elvitegravir 150 mg/cobicistat 150 mg/tenofovir alafenamide 10 mg/emtricitabine 200 mg | $3394 | $4073 |
| Scribil (EVG/c/TDF/FTC) | Elvitegravir 150 mg/cobicistat 150 mg/tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg | $3560 | $4272 |
| Triumeq (DTG/ABC/3TC) | Dolutegravir 50 mg/abacavir 600 mg/lamivudine 300 mg | $3182 | $3818 |
| INSTI plus one NRTI | | | |
| Dovato (DTG/3TC) | Dolutegravir 50 mg/lamivudine 300 mg | $2527 | $3033 |
| INSTI plus one NNRTI | | | |
| Juluca (DTG/RPV) | Dolutegravir 50 mg/rilpivirine 25 mg | $2982 | $3579 |

*Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf. Accessed (9/14/2021) [Table 22b].
Effect of STR on prevention of drug resistance

A potential advantage of STR is lower risk of selective non-adherence to components of the regimens. It is difficult to ascribe an effect of STRs on prevention of drug resistance, as it is a function of robustness of the regimen itself and adherence with the prescribed regimen. Nevertheless, an analysis of 168 participants with treatment-emergent drug resistance from eight cohorts and four randomized clinical trials suggests that STR can reduce the risk of resistance. In this analysis, compared to patients receiving Atripla, those receiving the same components individually in a non-STR regimen had a statistically significantly greater risk (53.4% in the STR group vs. 74.2% in the non-STR group) of selecting drug resistance mutations at virologic failure [18]. However, A Center for AIDS Research Network of Integrated Clinical Systems (CNICS) observational study found no significant difference in the risk of virologic failure with STR of Atripla when compared to MTR of its individual components in those newly initiating therapy [19], although there was a trend towards more virologic failure and M184V mutations among persons initiating MTR. Although not directly attributable to STR, the frequency of transmitted drug resistance (TDR) overall and as a function of robustness of the regimen itself and adherence with the prescribed regimen. Nevertheless, an analysis of 168 participants with treatment-emergent drug resistance from eight cohorts and four randomized clinical trials suggests that STR can reduce the risk of resistance. In this analysis, compared to patients receiving Atripla, those receiving the same components individually in a non-STR regimen had a statistically significantly greater risk (53.4% in the STR group vs. 74.2% in the non-STR group) of selecting drug resistance mutations at virologic failure [18]. However, A Center for AIDS Research Network of Integrated Clinical Systems (CNICS) observational study found no significant difference in the risk of virologic failure with STR of Atripla when compared to MTR of its individual components in those newly initiating therapy [19], although there was a trend towards more virologic failure and M184V mutations among persons initiating MTR. Although not directly attributable to STR, the frequency of transmitted drug resistance (TDR) overall and for individual drug classes have remained stable in the United States during 2014–2018 with <1% TDR prevalence for INSTI with increasing use of STRs.

Treatment simplification-switch studies to STRs

Many studies have established the efficacy of switching ART to STRs. These are summarized below.

Simplifying ART to 3-drug containing STRs

- Switch to efavirenz (EFV)-containing STR (Atripla): A randomized, controlled open-label switch study to simplify treatment to a STR of EFV/TDF/FTC demonstrated non-inferiority at 48 weeks for virologic suppression when compared to those who remained on their baseline regimen, similar discontinuation rates, and had the added benefit of decrease in fasting triglycerides [20]. The EFV/TDF/FTC STR was considered easier to follow than prior regimens by 97% and 96% of patients previously receiving PI-based and NNRTI-based therapies, respectively. Overall, 91% of those switched to EFV/TDF/FTC indicated a preference over their prior therapy in patient reported outcome measures [21].

- Switch to rilpivirine (RPV)-containing STR (Complera, Odefsey): Switching from EFV/TDF/FTC to RPV/TDF/FTC (GS-366–1160) or RPV/TAF/FTC (GS-366–1160) was a safe and effective option for virologically suppressed patients with EFV intolerance wishing to remain on an STR [22,23]. Tolerability and safety were also demonstrated for switching from nevirapine to a RPV STR in Rwandan adults, and additional benefit of lipid reduction in switching from a boosted PI-containing regimen to an RPV STR in the SPIRIT study.

- Switch to doravirine (DOR)-containing STR (Delstrigo): The DRIVE SHIFT open-label trial included switch from boosted PI- or elvitegravir- or NNRTI-based regimen to co-formulated DOR/TDF/3TC. Of the individuals taking the DOR STR, 91% (406 of 447) had an HIV-1 RNA level below 50 copies/ml at 48 weeks. Lipid parameters improved after the switch to DOR STR for those participants taking a boosted PI regimen at baseline [24].

- Switch to dolutegravir (DTG)-containing STR (Triumeq): The STRIVIVING (switch to DTG/ABC/3TC STR) open-label trial showed 83% and 92% of participants from the early switch and late switch groups, respectively, maintained virologic suppression at 48 weeks [25]. Adverse events and treatment discontinuations for side effects were more frequent in those who switched to the DTG-containing STR, although overall treatment satisfaction was reported higher in this group.

- Switch to bictegravir (BIC)-containing STR (Biktarvy): More recently, additional data is accumulating for maintained virologic suppression with switch to the once-daily STR of BIC/TAF/FTC from a boosted PI-based regimen consisting of atazanavir (ATV) or darunavir (DRV) plus either FTC/TDF or ABC/3TC [26], and also for those over 65 years of age switching from EVG/c/TAF/FTC or a TDF-based complete treatment regimen [27].

Simplifying ART to 2-drug containing STR

The FDA has approved the following 2-drug STRs as maintenance regimens in persons with suppressed HIV-1 RNA levels: oral dolutegravir and rilpivirine (DTG/RPV; Juluca) (supportive data from SWORD-1 and 2) [28] and oral dolutegravir and lamivudine (DTG/3TC; Dovato) with supportive data from ASPIRE [29] and LAMIDOL [30]. The two drug containing STR are recommended for those with suppressed HIV-1 RNA levels on a stable antiretroviral regimen, no history of treatment failure, and no known substitutions associated with resistance to the individual components of the 2-drug regimen.

Treatment simplification STR options for prior resistance

NNRTI and elvitegravir based 3-drug STRs have traditionally required a fully active NRTI backbone for durable
virologic suppression. Clinical trials in which patients are switched to STR maintenance therapy generally employ stringent inclusion criteria. These criteria preselect for patients who have a history of excellent adherence to therapy, few (if any) virologic failures, and overall high likelihood of virologic suppression after a switch. With the advent of dolutegravir and bictegravir which have a higher barrier to resistance, STR eligible populations are expanding to those with some selected drug resistance mutations or known prior virologic failure. In a randomized study of 1:1 switch to BIC/TAF/FTC or DTG + TAF/FTC once daily for those with ≥6 months of virologic suppression on dolutegravir based regimen, virologic suppression was maintained at 48 weeks [31]. 25% had NRTI resistance due to either prior virologic failure or treatment with non-suppressive single or dual NRTI-based therapies including 6% with K65R/E/N or ≥3 TAMs and no treatment-emergent resistance was detected.

**Lower prescription error rates**

Prescription errors in ART are common and often go undetected. In one review, antiretroviral errors were identified for 35% of all hospital admissions over a 3 year study period. Medication omission accounted for the majority of ART errors (69.2%), followed by dosing errors (14.6% combined under dose and overdose) and incorrect scheduling (13.1%) [32]; conversely co-formulated drugs protected against error (RR 0.66; 95% CI 0.50–0.88) and STR should potentially eliminate these prescribing errors.

Outpatient pharmacy fill errors for chronic diseases are common but not systematically documented. Usual errors include missing refill prescription or pharmacy dispensing error with omission of a component of MTR which can be obviated with co-packaging or STR. Some insurers limit ART drug dispensing to 30-day supply at a time and do not allow early refill which is not only burdensome and inconvenient but also raises the risk of drug resistance if MTR is on an unsynchronized refill schedule.

**Potential cost savings with STR**

Cost containment of antiretroviral drugs has been suggested by substituting generic individual components instead of branded STR. Prescription drug pricing is exceedingly complex in the United States and mostly opaque to health care providers as costs differ by state, commercial versus government programs, insurance negotiated costs and formulary and varies for individual patients based on their insurance plan cost sharing which can be copayments, coinsurance or insurance deductible or out-of-pocket limits. Usually, STRs confer direct cost benefit to individual patients as there is a single copayment. In addition, there are typically manufacturer rebates for branded STR products that help offset out-of-pocket cost or AIDS Drug Assistance Program (ADAP) that allow premium and copayment cost sharing for eligible patients. Lower priced STR including efavirenz-containing generic STR and two-drug STR are available (Table 1), which may be appropriate for selected patients.

Inarguably, there is societal cost savings using generic MTRs. A mathematical simulation model based on 2009 U.S. data suggested that switching all patients in the U.S. from the branded STR EFV/TDF/FTC to a three pill daily regimen of generic EFV, 3TC, and branded TDF would have saved almost $1 billion per year with only a small decrement in virologic efficacy [33]. An analysis of switching from branded co-formulated DTG/ABC/3TC to branded DTG plus generic ABC and generic 3TC suggests a 25% reduction in both the wholesale acquisition cost (generating savings of $667) and the federal supply schedule cost (generating savings of $553) for a 30-day supply [34].

De-simplifying STRs to two or three tablets once-daily regimens for cost savings was attempted in Calgary, Canada [35], France [36], and Denmark [37]. In these health care systems which emphasize health expenditure savings and societal altruism, de-simplification was accepted by ~ 50% of patients approached in the Canadian and French study with preference for STR cited for those declining de-simplification. There is a demonstrable patient preference for STRs with improved quality of life attributed to STRs as perceived by patients. An interesting analysis was done for the Italian health system to assess the economic value of a reduced number of pills. The STR corresponded to a €4541.00 lower cost-effectiveness ratio per quality-adjusted life-years versus the MTR, with a 17% lower cost in favor of the STR. In their analysis, a 24% price decrease for the MTR would make it comparable with that of the STR, identifying a potential maximum premium pricing of 29% assigned to STR over the corresponding non-combined components of the therapeutic regimen [38].

**Use of STR in challenging populations**

In comparison to adults, young people living with HIV have lower rates of adherence to ART and virologic suppression. A retrospective cohort study from 18 U.S. HIV clinics participating in the HIV Research Network found use of STR was associated with greater likelihood of viral suppression in treatment-naive youth with 84% of those on STR versus 67% of those on MTR achieving viral suppression ($P < 0.01$) at 12 months after initiating therapy.ART medication often unveils the HIV status in school, at home and in congregated settings eliciting stigma. Food neutral once a day STR allows ease of dosing and affords privacy. Housing instability inversely correlates with HIV virologic suppression. A prospective observational study assessed adherence and virologic response to EFV/TDF/FTC.
STR among a cohort of homeless and marginally housed individuals [40]. Adherence was higher in EFV/TDF/FTC STR compared to non-one-pill-once-daily therapy ($P = 0.006$) after controlling for multiple confounders.

**Summary and legacy**

A recent meta-analysis [41] again reconfirms that patients on STR have better adherence, lower rates of ART discontinuation, improved viral load suppression and fewer laboratory abnormalities than those on MTRs. Economic and humanistic outcomes clearly favor STR. Low- and middle-income countries (LMIC) have been disproportionately affected by the HIV pandemic but antiretroviral drugs remained out of reach for most living in developing countries in the first decade of ART. Indian generic manufacturers were the first to produce the FDC of stavudine, lamivudine and nevirapine, which was a first-line regimen recommended by the World Health Organization at the time, at a cost of less than 10 U.S. dollars a day in 2001 and was the mainstay of many treatment programs in developing countries. By the end of 2012, almost half of all people using ART in LMICs had TDF in their treatment regimen, and 50% used EFV. The National Institutes of Health and Gilead Sciences were the first licensors to join with TDF and FTC, with future rights to patents covering TDF and FTC, with future rights to patents covering elvitegravir, cobicistat, and Stribild.

John Martin was one of the major contributors to the design, development, and global impact of antiviral therapy and his legacy endures on the global HIV response today with the roll out of three-in-one, fixed-dose combination of TLD (TDF/3TC/DTG) in LMIC for HIV treatment and TDF/FTC and TAF/FTC use worldwide for HIV infection prevention. He leaves behind a profound and lasting legacy as a champion of human health.

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