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HIV TREATMENT OUTCOMES IN SOUTH AFRICA: FIXED-DOSE COMBINATION VS. TRADITIONAL MULTI-PILL ART

Background

Long-term antiretroviral therapy (ART) adherence is critical for achieving optimal HIV treatment outcomes[1-4]. The introduction of fixed-dose combinations (FDCs) where one pill contains multiple active drugs has simplified pill taking. This is achieved through a reduction in pill burden in combination with simpler scheduling (once daily)[5]. While the immunologic and virologic effects of FDCs appear positive, there is still limited data on the effects of FDCs administered to HIV positive individuals at scale, under routine clinic conditions[4].

In April 2013, South Africa began initiating eligible first-line patients on a once daily, single tablet FDC antiretroviral (ARV) regimen of tenofovir (TDF), emtricitabine (FTC) and efavirenz (EFV)[6]. To evaluate the impact of this policy change, we compared treatment outcomes among patients who initiated this FDC ARV regimen ≥5 month after FDCs became available, to patients who initiated a TDF, lamivudine (3TC) and EFV multi-pill ART regimen prior to FDC introduction at a large public-sector HIV clinic in Johannesburg, South Africa.

Methods

Design

We conducted a retrospective cohort study of patients, initiating first-line ART at Themba Lethu Clinic, located at Helen Joseph Hospital in Johannesburg, South Africa.

Study Population

Table 1. Cohort description

	Cohort description	
Selection criteria	**FDC cohort**	**Multi-pill cohort**
Enrolment period	1 September 2013 – 31 August 2014	1 September 2011 – 31 August 2012
Regimen	TDF+FTC+EFV (fixed-dose combination)	TDF+3TC+EFV
Pill number	1 pill per day	3-5 pills per day

Patients were excluded from the study if they were pregnant or had tuberculosis (TB).

Outcomes

We assessed the following outcomes: 1) attrition (a combination of all-cause mortality/death and lost to follow-up [LTFU], defined as being >3 months late for the last scheduled visit with no subsequent visit[7, 8]; 2) missing a medical visit (0 vs. ≥1) defined as being >7 days late for a scheduled medical visit[9]; and 3) virologic suppression defined as a viral load <400 copies/mL at 6 and 12 months post-ART initiation (+/- 3 months). Person-time accrued from ART initiation to the earliest of: 1) attrition; 2) transfer out to another facility; 3) completion of 12 months of follow-up.

Cox proportional hazards models were used to evaluate the relationship between FDCs vs. multiple pills and attrition. Poisson regression was used to estimate the association between FDCs vs. multiple pills for both missed medical visits and virologic suppression.

Ethical considerations

Ethical approval for the use of data was provided by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M140201). The study protocol was reviewed by the Institutional Review Board of the University of Witwatersrand who approved collection of the data without informed consent and use of an anonymous analytical data set.

Results

Baseline characteristics

We included 3151 patients in our analysis. 2230 (70.8%) initiated multi-pill ART and 921 (29.2%) initiated on a FDC. Patient characteristics did not differ substantially between patients on a multi-pill regimen compared to a FDC apart from a marginally higher median CD4 cell count at ART initiation (175.5 vs. 158.0 cells/mm³ respectively), while a lower proportion of the former initiated with CD4 cell counts >350 cells/mm³ (4.3 vs. 10.8%). In both groups, close to two thirds were female (59%), median age was 38 years, and median haemoglobin was 11.8 g/dL.

Attrition

By 12 months on ART, the overall incidence of attrition was 17.5% (552/3151) (11.9% were LTFU and 5.6% had died). Adjusted analyses reveal that patients on a FDC

have approximately the same risk of attrition by 12 months compared to those on multi-pills (aHR: 0.98; 95% CI: 0.77–1.24) (Table 2).

Missed medical visits

By 12 months on treatment, a lower proportion of those taking FDCs (11.3%) missed at least one medical visit compared to those taking multiple pills (17.5%). Similarly, in adjusted analyses, patients initiated on a FDC had a 34% lower risk of missing at least one medical visit (aRR: 0.66; 95% CI: 0.52–0.83) (Table 2).

Virologic suppression

At 6 months, 70% (647/921) of those who initiated FDC treatment vs. 66% (1465/2230) in the multi-pill group had viral load tests. At this time point, virologic suppression was marginally higher among those taking FDCs (83 vs. 77%; aRR: 1.10; 95% CI: 0.99–1.23) (Table 2).

At 12 months, 31% (220/717) of those taking FDCs vs. 33% (553/1657) of those taking multiple pills had viral load tests. Similar to viral load suppression at 6 months, patients on a FDC who had a viral load test were marginally more likely to achieve viral suppression by 12 months on treatment (aRR: 1.12; 95% CI: 0.92–1.36) (Table 2).

Table 2. Adjusted estimates of the relationship between multi-pill initiation and fixed-dose combination initiation on primary outcomes

Primary outcomes				
	Attrition by 12 months	**Missed medical visits by 12 months**	**Virologic suppression at 6 months**	**Virologic suppression at 12 months**
	n=312/ 2226	**n=394/ 2511**	**n=1440/ 1828**	**n=498/ 651**
Variable	aHR[a] (95% CI)	aRR[b] (95% CI)	aRR[c] (95% CI)	aRR[c] (95% CI)
Multi-pill	1.00	1.00	1.00	1.00
FDC	0.98 (0.68-1.00)	0.66 (0.52-0.83)	1.10 (0.99-1.23)	1.12 (0.92-1.36)
aHR Adjusted hazard ratio; aRR Adjusted relative rate, FDC fixed-dose combination BMI body mass index, WHO World Health Organization				
[a]Model adjusted for the following variables at ART initiation: regimen type, sex, age, CD4 cell count, anaemia, BMI, and WHO stage				
[b]Model adjusted for the following variables at ART initiation: regimen type, sex, age, CD4 cell count, and WHO stage				
[c]Model adjusted for the following variables at ART initiation: regimen type, sex, age, CD4 cell count, and WHO stage				

Policy Relevance

Currently, there are a limited number of studies focusing specifically on the effects of active ARV drugs administered as separate pills compared to those same active drugs administered in a fixed dose combination[5]. Thus the current study helps fill a critical gap in literature. Our results suggest that under programmatic conditions, FDCs achieve similar outcomes in terms of attrition and virologic suppression compared to a multi-pill regimen. However, FDCs may have an important role to play in supporting patient monitoring and adherence through improved clinic attendance via medical visits. In our study, patients initiating ART on a FDC were less likely to miss medical visits in the first 12 months on treatment. While the exact mechanisms through which a simpler ART regimen may improve clinical attendance needs further exploration, the improved monitoring may be a useful outcome among patients initiating treatment on newer more relaxed ART guidelines such as Universal Test and Treat (UTT). Moreover, our results represents evidence which support current and possibly future South African HIV policy, particularly in light of newer dolutegravir (DTG) based first-line FDC ART which not only proves more cost-effective but also more efficacious than current first-line FDCs[10].

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