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SHORT COMMUNICATION

Dual therapy with renally adjusted lamivudine and dolutegravir: a switch strategy to manage comorbidity and toxicity in older, suppressed patients?

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Objectives
The aim of the study was to evaluate the efficacy of dual therapy with lamivudine (3TC), with dose adjustment for renal function, and dolutegravir (DTG) in a subgroup of patients fully suppressed on treatment who were switched because of concerns about comorbidity and toxicity on their current triple drug regimen.

Methods
A retrospective evaluation of clinical and pathological parameters from an electronic patient record from a single centre was carried out.

Results
There were no virological failures in 52 patients with a median age of 60.5 years. The median duration of follow-on dual therapy was 2.29 years (28 months; range 1.10–3.34 years). In 25 of 52 (48%) cases, the dose of 3TC was adjusted taking into account reduced renal function, and none of these patients experienced virological failure. Four additional patients discontinued early, because of side effects of the switch, with no failure.

Conclusions
This retrospective review suggests that 3TC and DTG may be effective in controlling viral load in older patients with comorbidities. This regimen appears to be a useful option in the context of comorbidities (including renal impairment) and polypharmacy in older patients. However, this review has been conducted in one centre and in a small population of patients. Therefore, further multicentre trials involving larger populations of patients are needed.

Keywords: dolutegravir, dose adjustment, dual therapy, lamivudine, observational, simplification

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Introduction

The life expectancy of people living with HIV has improved dramatically with the advent of effective therapy and an increasing proportion of people are aged 50 years or older. The requirement for lifelong therapy and the management of non-HIV-related comorbidities has become increasingly important as patients are living well with HIV. As a result, there is more interest in simplified antiretroviral therapies (ARTs) that are efficacious, well tolerated, and free from drug interactions.

Dual therapy as maintenance is an approach that is being evaluated as a means of reducing potential side effects and increasing tolerability by reducing the number of agents, as well as reducing drug–drug interactions. Data have been reported on the use of dolutegravir (DTG) combined with rilpivirine (RPV) [1] and lamivudine (3TC) [2].

The analysis of 48-week data from the GEMINI 1 and 2 studies, investigated DTG and 3TC in ART-naïve patients, demonstrated noninferiority of this regimen when compared with DTG and tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC). Good tolerability was also demonstrated.

The aim of this review was to assess the efficacy, durability and tolerability of simplifying to once a day (OD) therapy with DTG and 3TC in a real-life cohort of

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patients on fully suppressive ART and switched for the purposes of simplification or because of toxicities or comorbidities. This cohort is of interest as 3TC was used in an adjusted dose according to renal function, and this cohort included individuals who may have been deemed ineligible for prospective clinical trials.

Methods

This was a retrospective survey of electronic records of patients receiving DTG and 3TC conducted in a single urban UK centre with an HIV-infected cohort of approximately 1100 patients.

Patients were switched to dual therapy for a comorbidity, drug interaction or side effect from their baseline ART (Table 1). A proportion were selected for DTG and renally adjusted 3TC, where there were concerns regarding renal function [based on estimate glomerular filtration rate (eGFR)] as measured by CKD-Epi (Chronic Kidney Disease – Epidemiology collaboration equation) (mL/min/1.73 m^2), i.e. eGFR was < 50 mL/min/1.73 m^2. This treatment was initiated prior to the general availability of tenofovir alfenamide (TAF) at this centre.

Table 1 Reasons for drug switch and prior ART therapy

Reasons for drug switch to dual therapy	
eGFR	12
Proteinuria	3
Tolerability/side effects	8
Cardiovascular risk	6
Interactions	11
Hyperlipidaemia	24
Simplification/pill burden	4
No information available	1
Lamivudine dose adjustment [*n* (%)]	
300 mg	27 (52)
150 mg	24 (46)
50 mg	1 (2)

Previous ART prior to switch

ART	Number of patients
Tenofovir disoproxil fumarate	36
Abacavir	35
Zidovudine	19
Efavirenz	27
Nevirapine	10
Rilpivirine	10
Integrase inhibitors	
Raltegravir	17
Dolutegravir	6
Elvitegravir	0
Boosted regimens	
Atazanavir with ritonavir	16
Darunavir with ritonavir	25
Lopinavir with ritonavir	5

ART, antiretroviral therapy; eGFR, estimated glomerular filtration rate.

Data that were collected included age and gender; presence of concomitant disease and side effects of previous ART regimens such as abnormal laboratory test results, adverse events and presence of drug interactions; the duration and choice of ART at baseline and earliest date of viral failure (i.e. two or more consecutive viral loads > 40 HIV-1 RNA copies/mL prior to and after starting dual therapy); date started ART and most recent CD4 count. The pre switch eGFR readings were taken between 2 and 6 months prior to the visit the switch occurred, and post switch eGFR readings are most recent reading. Patients with an eGFR > 90 mL/min/1.73 m^2 were recorded as having an eGFR of 90 mL/min/1.73 m^2.

Results

Between 2015 and 2019, 56 patients switched to dual therapy consisting of DTG 50 mg OD and 3TC. The full dose of 3TC was 300 mg, and the renally adjusted doses were 150 and 50 mg. Patient demographic data in Table 2 show that the median age was 60.5 years, and the median time on previous ART was 9.4 years, with a range of 0.80–26.1 years. There were no viral failures in these patients.

Of 56 patients switched, four patients discontinued dual therapy for side effects; they had a follow-up time of < 1 year and were on dual therapy for a median of 2 months before discontinuing. One of the four was on a renally adjusted dose of 3TC. These four patients experienced known side effects of DTG. Two patients experienced severe headaches, one insomnia and the other vivid dreams, disturbed sleep, muscle pain and bloating.

Table 2 Baseline demographics and patient characteristics of 52 patients

Gender [*n*/total (%)]	
Male	44/52 (85)
Female	8/52 (15)
Age (at switch) [*n*/total (%)]	
< 30 years	0
30–< 40 years	1
40–< 50 years	9
50–< 60 years	17
60–< 70 years	13
≥70 years	12
CD4 count (most recent, at time of data collection) [*n*/total (%)]	
< 200 cells/μL	0
200–350 cells/μL	3
> 350 cells/μL	49
Not available	0
HIV risk acquisition [*n*/total (%)]	
Heterosexual	24 (46)
Homosexual	26 (50)
Injecting drug use	0 (0)
Other	2 (4)

The data for these four patients were therefore not included.

The other 52 patients had a follow-up period of > 1 year, and 25 of these patients were on a renally adjusted dose of 3TC. The median duration on dual therapy was 2.29 years (28 months; range 1.10–3.34 years); the most recent median CD4 count after switch was 737 cells/μL and there were no recorded viral failures. The median number of viral load measurements after starting dual therapy was 6. None of the 52 patients who continued (after 3 months) experienced side effects sufficient to merit a switch.

Overall, the median eGFR of the 52 patients before starting dual therapy was 62 mL/min/1.73 m^2, and the median of the most recent eGFR while on dual therapy was 61 mL/min/1.73 m^2. There were two patients who did not have any recorded eGFR within 6 months of starting dual therapy; therefore, they were not included in the median eGFR measurement. There were five patients who had an initial eGFR reading of > 50 mL/min/1.73 m^2 that fell below 50 mL/min/1.73 m^2 while on dual therapy, and the mean difference between measurements was 7.2 mL/min/1.73 m^2. Two of the five were put on renally adjusted 3TC. There was no significant change in mean unfasted cholesterol before (5.65 mmol/L) and after (5.16 mmol/L) dual therapy.

However, cholesterol would not be an accurate measure as these are unfasted retrospect readings, and factors such as being on a protease inhibitor and/or TDF previously may influence cholesterol levels.

For the 25 patients on renally adjusted 3TC, the median eGFR before starting dual therapy was 47 mL/min/1.73 m^2, and while on dual therapy, the median eGFR was 54 mL/min/1.73 m^2.

There was one patient on a smaller dose of 50 mg 3TC for 1.13 years, because the patient's initial eGFR before starting on dual therapy was 20 mL/min/1.73 m^2. After starting dual therapy, eGFR improved to 44 mL/min/1.73 m^2.

For the remaining 26 patients on full-dose 3TC, the median eGFR before starting dual therapy was 62 mL/min/1.73 m^2, and after starting dual therapy, the median was 61 mL/min/1.73 m^2.

There was one viral blip (for full-dose 3TC), with full subsequent suppression, and one death, which was not HIV related.

Additional data on eGFR are presented in Table 3 to show the effects of treatment change on eGFR (starting DTG/stopping TDF).

Discussion

This retrospective case-note review provides further evidence that DTG and 3TC could be a robust regimen in a real-life clinical setting, as there was no evidence of virological failure in this case series with a median treatment duration of 2.5 years.

The GEMINI 1 and 2 trials [3] recruited 1441 patients, who were ART naïve, randomized to treatment with either dual therapy (3TC and DTG) or triple therapy (TDF, FTC and DTG).

The mean age was 32.5 years, with only 9% and 11% (in respective arms) aged > 50 years. Therefore, the otherwise excellent GEMINI trial does not include a high proportion of older, treatment-experienced patients who arguably have most to gain from treatment simplification with a two-drug regimen. Patients with existing comorbidities might be taking other medication and would probably benefit from a regimen including DTG in order to minimize potential drug–drug interactions.

In common with data from other interventional trials, the GEMINI trial data may not represent current populations of people receiving care for HIV infection, with the median age of people receiving care for HIV infection in the UK increasing from 40 years in 2008 to 46 years in 2017. In 2017, more than a third of people receiving HIV care in the UK were aged > 50 years [4] (2018 Report). Similarly, the EUROSIDA HIV-infected cohort has also seen an increase in age to a median of 48.6 years in 2014 and an increase in comorbidities [5].

A multicentre study in Italy by Borghetti *et al.* [2] looked at 206 patients stable on combination ART (cART) with a median age of 51 years who were switched to 3TC and DTG primarily for simplification (31%) or toxicity

Table 3 Effects of treatment change on estimated glomerular filtration rate (eGFR)

Drugs	Median eGFR before dual therapy (mL/min/1.73 m^2)	Median eGFR after dual therapy (mL/min/1.73 m^2)
All patients (including those with previous ART containing DTG) (n = 52)	54	54
Patients without previous ART containing DTG (n = 46)	64	60
All patients (including those with previous ART containing TDF) (n = 52)	54	54
Patients without previous ART containing TDF (n = 16)	63	62

The pre switch eGFR readings were taken between 2 and 6 months prior to the visit the switch occurred, and post switch eGFR readings are most recent reading.
ART, antiretroviral therapy; DTG, dolutegravir; TDF, tenofovir disoproxil fumarate.

(54.4%). This is the largest cohort to date and the study similarly reported no virological failures, an absence of toxicity and improvements in CD4 count, CD4:CD8 ratio, lipid profile and eGFR. In this cohort, the median age was 51 years and it was much more representative of people receiving care for HIV infection in Europe. The renal dose adjustment for 3TC was not noted.

We acknowledge the limitations of these data, which were retrospective and included patients with a range of comorbidities and toxicity issues. However, this is the first data series that suggests that a dose adjustment of 3TC for reduced renal function does not appear to affect the virological outcome, albeit for a limited sample size.

These data add value to existing evidence. Our cohort were older, with an average age of 60.5 years compared to 32.5 years (GEMINI 1 and 2) [3], 48.6 years (EUROSIDA HIV) [5] and 51 years (Borghetti *et al*. [2]). Our cohort were medically complex with additional diagnoses of diabetes, hyperlipidaemia, and declining renal function, similar to the EUROSIDA HIV [5] and Borghetti *et al*. [2] case series. Lastly, our cohort had a longer duration of treatment than previously reported series, of 28 months (112 weeks) compared to 48 weeks (GEMINI 1 and 2) [3] and 96 weeks (Borghetti *et al*. [2]).

This combination could provide an alternative, in some patients, to switching to TAF.

Questions remain as to the long-term safety of such a regimen and its efficacy at privileged sites, such the central nervous system, and this treatment regimen requires further investigation and long-term follow-up.

Conclusions

This case series suggests that switching to dual therapy with 3TC and DTG is well tolerated, durable and efficacious in this population with a median age of 60.5 years in a real-life clinical setting, even on a renally adjusted 3TC dose.

This dual therapy could be considered as a promising potential alternative where there are specific medical needs; to avoid interactions, toxicities and effects of comorbidities in an ageing HIV-infected cohort, especially as patients could stand to benefit from treatment simplification. Further research is needed.

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