Simplified HAART (Kaletra in Mono and Dual Therapy) – A Retrospective Review (the KIMODO Study)

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Background

With the advent of HAART, the treatment of HIV/AIDS has changed to the management of a chronic illness[1]. However, as long-term therapeutic success has become a realistic goal of treatment, there are increasing reports of toxicities associated with therapy. In addition, a high degree of compliance with treatment regimens is necessary for the success of HAART but adherence with multiple medications has been shown to decrease with time, leading to virological failure[2,3].

These factors have generated interest in exploring less toxic, simpler, more compact and less expensive treatment strategies. Kaletra™ (lopinavir/ritonavir; LPV/r) is a boosted PI with a high genetic barrier to resistance[4] which allows high plasma levels of lopinavir to be reached[5] and as such the potential for failures due to sub-therapeutic drug concentration levels are reduced.

Methods

Study Design

- This study was a multi-centre, retrospective chart review of subjects' medical notes. Subjects already on Kaletra as either monotherapy (Kaletra only) or dual therapy (Kaletra plus one other agent) for the treatment of HIV infection were recruited to take part.
- Data was collected from at least two routine clinic visits prior to treatment simplification, but no earlier than January 2001, to the last routine clinic visit prior to data collection.

Entry Criteria

- HIV positive patients at least 18 years of age who have already been prescribed Kaletra as either a single agent or as part of a two drug HAART regimen.

Study Objectives

Primary objective:

- To investigate the prevalence of patients suppressing viral replication to < 50 copies/ml.

Secondary objectives:

- To investigate the prevalence of continued immunologic restoration.
- To determine resistance patterns and genotypic mutations in subjects who experience virological failure.

Statistical analysis

- Analyses were performed on all subjects with data for a minimum of 6 months following simplification.
- Descriptive methods only were used to summarise the data with no significance testing. Continuous data was summarised with the usual summary statistics and categorical data by a frequency distribution. Baseline was defined as the last visit prior to the change to simplification.
- Data were summarised for all patients, type of simplification (monotherapy/dual therapy/both), age, baseline viral load, baseline CD4, success/failure and stop/continue. Dual therapy patients were divided into different drug classes depending upon the second drug in the regimen (NRTI, NNRTI, PI or a mixture).
- Failure of simplification was defined as two consecutive viral loads of > 400 copies/mL following a fall to <50 copies/mL during simplification OR all values ≥ 50 copies/mL throughout simplification (success/failure subgroups).
- Data were also defined by whether simplification was stopped or ongoing at the end of the follow-up (stop/continue subgroups).

Results

131 Patients were included from 7 UK sites

Table 1. Baseline characteristics

Number of subjects	Median Age (years)	Gender	Race	HIV risk Factor	CDC classification at baseline
131	44	109 Male 22 Female	99 Caucasian 27 Black 5 Other	89 MSM 12 Partner positive 10 IVDU 14 Other/unknown	42 AIDS 42 Symptomatic 47 Asymptomatic

Table 2. Baseline viral load and CD4+ values

	Parameter	Value
Baseline CD4+ count	Median CD4+	310 x 10^6 c/mm^3
	Median CD4+ nadir	140 x 10^6 c/mm^3
	% > 350 x 10^6 c/mm^3	45%
Baseline viral load	< 50 c/mL	50%
	50 – 400 c/mL	8%
	> 400 c/mL	42%

Table 3. Baseline mutations per simplification regimen (%)

	NRTI mutations	NNRTI mutations	PI mutations
Monotherapy	48	31	21
Dual therapy	44	31	13
Mixed	40	20	0
NNRTI	14	0	3
NRTI	67	67	33
PI	71	54	17
Both	44	22	11

Table 4. Anti-retroviral Treatment (ART) History

Baseline drug experience	Number of subjects (%)
NRTI/NNRTI/PI	60 (46)
NRTI/NNRTI	18 (14)
NRTI/PI	29 (22)
NRTI	5 (4)
ART naïve	19 (15)

Table 4. Type of simplified treatment

Type of simplified regimen	Number of subjects (%)	
Monotherapy (Kaletra only)	52	(40)
Dual therapy (Kaletra plus one other drug)	70	(53)
Mixed	5	(4)
NNRTI	29	(22)
NRTI	12	(9)
PI	24	(18)
Both (periods of mono- and dual therapy)	9	(7)
Total	131	(100)

Results *(continued)*

Table 5. Reasons for simplification

	Percentage of all patients
Toxicity	31%
Lack of efficacy	15%
Resistance	13%
Poor compliance	8%
Other	68%
Decreased pill burden	4%
Patient choice/request	5%
To simplify regimen	11%

Table 6. Median time on simplified therapy

	Time (months)	
All	16.57	n=131
Monotherapy	14.1	n=52
Dual therapy	17.47	n=70
Mixed	23.57	n=5
NNRTI	15.57	n=29
NRTI	18.32	n=12
PI	24.27	n=24
Both	24.37	n=9

Study endpoints

- Primary endpoint:
  At last visit on simplified therapy, 79.4% of patients had a viral load < 50 c/mL

  16 patients (12.2%) reached the definition of virologic failure:
  Monotherapy 7 (13.4% of total mono)
  Dual therapy 9 (12.8% of total dual)

  32 patients (24.4%) stopped simplified therapy during the study: 10 (19%) in the monotherapy arm and 20 (29%) in the dual therapy arm. The main reasons for discontinuing a simplified regimen in these patients were lack of efficacy (28%), toxicity (25%), poor compliance (9%) and other (44%).

- Secondary endpoints:
  Median CD4+ cell count increase from baseline for (Fig 2):
  All patients 130 c/uL.
  All dual 197 c/uL
  Mono 54 c/uL

Figure 1. Viral load disposition first 24 months

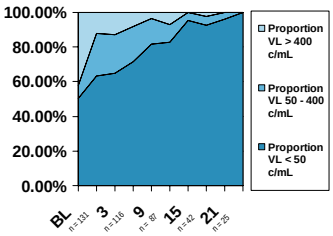
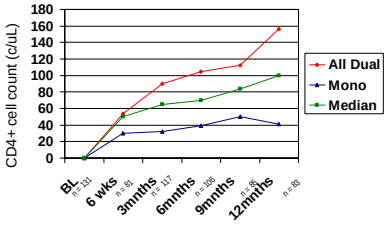


Figure 2. CD4+ cell count change from baseline



4 Subjects with available data exhibited new primary mutations during/after simplification.
All 4 subjects reached the definition of virologic failure and all 4 subjects stopped their simplified regimen.

Table 7. Subjects with new mutations compared with baseline

	NRTI mutations	NNRTI mutations	PI mutations
Subject 109 (no baseline test available)	M41L D67N K70R M184V T215Y K219Q	K103N	L10F/I K20R/M/I M36I/V I54V A71V V82A/F/T/S L90M
Subject 304 (no baseline test available)	None	V106A Y181C	A71V V77I
Subject 609	K70R	None	None
Subject 715	M184V	None	L10F/I M46I

Table 8. Selected baseline characteristics by treatment success/failure

	Success (n=115)	Failure (n=16)
Baseline CDC classification		
AIDS	28%	63%
Symptomatic	33%	25%
Asymptomatic	39%	12%
Median highest baseline VL	174 662 c/mL	189 721 c/mL
Median CD4+ nadir	140 c/uL	100 c/uL
3 Class experienced	42%	75%
Reason for simplification		
Toxicity	29%	44%
Poor compliance	4%	31%

Conclusions

- In routine clinical practice, some patients receive treatment with Kaletra as part of a mono- or dual therapy regimen.
- In KIMODO, reasons for change to a simplified regimen were variable and included drug toxicity, lack of efficacy and drug resistance.
- Overall, a simplified regimen containing Kaletra was efficacious with 79% of patients achieving an undetectable viral load at last visit with 12% of patients reaching the definition of virologic failure. Median increase in CD4+ cell count from baseline was 130 c/uL with the dual therapy patients doing better with regard to CD4+ cell recovery compared to monotherapy.
- Four patients with available data exhibited new mutations during or after simplified therapy (3 NRTI, 2 NNRTI and 3 PI). Two of these patients had no baseline resistance tests available and are assumed to have had no resistance mutations prior to simplification.
- Factors that were associated with a risk of failure of simplified therapy included baseline CDC classification of AIDS, a higher median baseline viral load, a lower CD4+ cell count nadir, previous 3-class drug experience and if the reasons for simplification was drug toxicity or poor patient compliance.

References

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