

Stability of Didanosine and Stavudine Pediatric Oral Solutions and Kaletra™ Capsules at Temperatures From 4°C to 55°C For 8-12 Weeks

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Background: Refrigeration is recommended for didanosine (ddl) and stavudine (d4T) pediatric oral solutions and Kaletra (LPV/RTV) capsules. Data are lacking regarding their stability at non-refrigerated temperatures. These drugs are increasingly prescribed for patients in the developing world, many of whom lack access to refrigeration and live in climates with temperatures that can exceed 40C. We examined the stability of these drug formulations after storage under experimental conditions for up to 11 weeks at temperatures up to 55C.

Methods: Ddl and d4T were reformulated according to manufacturer's instructions. One mL aliquots of each drug were kept at 4C, 15C (d4T only), 25C, 35C, 45C, and 55C. Ddl and d4T stability at each temperature was tested on day 1, and at 1, 2, 4 and 8 weeks. LPV and RTV were assayed from Kaletra capsules stored at these same temperatures for 11 weeks. Three aliquots were tested at each temperature and time point. Ddl, d4T and Kaletra (LPV/RTV) were assayed using reversed-phase high-performance liquid chromatography (HPLC) with UV detection. The 3 results for each drug and time point were averaged; the average area of drug peak at one temperature and time point is expressed as a percentage difference from the drug peak area of stock solution kept at 4C for the same time point.

Results: Ddl was stable through week 4 at temperatures to 45C. At week 8, the change in ddl drug peak area compared with the 4C control was negligible at 35C or less, but was -16.0% at 45C and -58.1% at 55C. D4T was stable at 8 weeks only if stored at 10C or less (d4T drug peak area was -19.9% after 8 weeks at 15C). D4T was stable at 4 weeks only if stored at 25C or less (d4T drug peak area was -16.6% and -83.9% for drug stored at 25C and 35C, respectively. After 4 weeks at these temperatures, the d4T drug peak area was -31.3% and -95.8%, respectively (and at 8 weeks, -52.8% and -99.9%). For Kaletra, LPV and RTV loss were negligible for temperatures to 35C at 11 weeks. At 11 weeks, LPV drug peak area was -13.1% at 45C and -18.2% at 55.0C, and RTV drug peak area was -42.5% at 45C and -61.3% at 55C.

Conclusions: Ddl pediatric oral solution is stable at temperatures up to 35C for 8 weeks. D4T solution, however, shows significant loss of stability after 4 weeks at 25C, and the majority of drug is lost after even 1 week at 35C. The LPV component of Kaletra is stable at temperatures to 45C for 11 weeks, and the RTV component is stable at temperatures to 35C for 11 weeks.

Background

- ddl and d4T pediatric oral solutions and Kaletra™ capsules are prescribed with increasing frequency in the developing world
 - Often used in warm climates
 - Refrigeration rarely available
- Refrigerated storage (2-8°C) is recommended for these drug formulations (or storage up to 25°C for Kaletra™)
- Published data are lacking on stability of these formulations at non-refrigerated temperatures

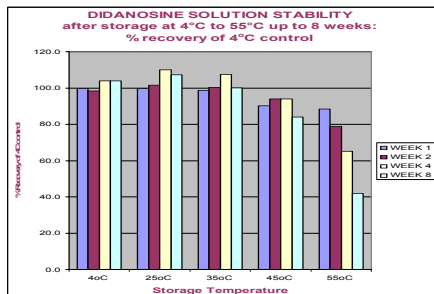
Methods

- ddl and d4T solutions and Kaletra™ capsules stored at 4°C, 25°C, 35°C, 45°C, and 55°C (d4T also at 10°C & 15°C)
- ddl and d4T tested after storage at these temperatures for 1, 2, 4 and 8 weeks (also after light exposure and storage at 4°C / 25°C fluctuating temperature for 8 weeks)
- Lopinavir (LPV) and ritonavir (RTV) tested after Kaletra™ capsules stored at these temperatures for 11 weeks
- Stability assayed with reversed-phase high-performance liquid chromatography (HPLC) with UV detection
- Three aliquots of each drug tested at each temperature and time point, results averaged
- Percent drug recovery calculated from average drug peak area divided by peak area of control sample (stock solution / capsule kept at 4°C for the same duration)

Conclusions

- ddl pediatric oral solution is stable at temperatures up to 35°C- 45°C for at least 8 weeks
- d4T oral solution shows considerable instability after 4 weeks at 25°C, and most of the drug is lost after even 1 week at 35°C
- As formulated in Kaletra™ capsules, LPV is stable at temperatures to 35°C- 45°C and RTV at 35°C for at least 11 weeks

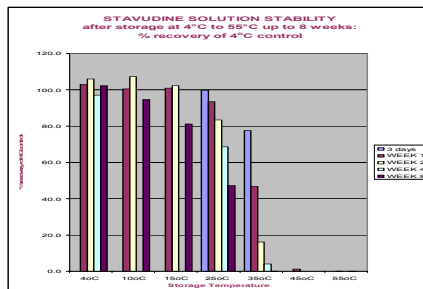
Results



Percent change in ddl drug peak area compared with contemporaneous 4°C

Storage duration	4°C	25°C	35°C	45°C	55°C	25°C in light	4°C / 25°C fluctuating
1 WEEK	-0.2%	-6.4%	-1.4%	-9.9%	-11.5%	-	-
2 WEEKS	-1.5%	+1.5%	+0.3%	-0.6%	-21.0%	-	-
4 WEEKS	+3.9%	+10.0%	+7.4%	-6.0%	-34.9%	-	-
8 WEEKS	+3.9%	+7.3%	+0.2%	-16.0%	-58.1%	-1.1%	+6.4%

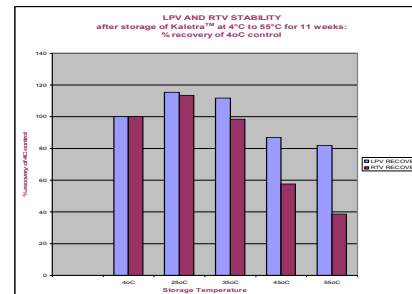
Results



Percent change in d4T drug peak area compared with contemporaneous 4°C control

Duration of storage	4°C	10°C	15°C	25°C	35°C	45°C	55°C	25°C in light	4°C / 25°C fluctuating
3 DAYS	0%	-	-	-0.2%	-22.3%	-	-	-	-
1 WEEK	+3.0%	+0.5%	+1.0%	-6.5%	-53.3%	-58.7%	-99.9%	-	-
2 WEEKS	+6.1%	+2.2%	-8.0%	-16.6%	-83.9%	-	-	-	-
4 WEEKS	-2.9%	-	-	-31.3%	-95.8%	-	-	-	-
8 WEEKS	-2.2%	-5.2%	-18.9%	-52.8%	-99.9%	-	-	-42.3%	-11.4%

Results



Percent change in LPV and RTV drug peak areas at 11 weeks compared with 4°C

Storage duration	4°C	25°C	35°C	45°C	55°C
Lopinavir	0%	+15.5%	+11.7%	-13.1%	-18.2%
Ritonavir	0%	+13.4%	-1.5%	-42.5%	-61.3%