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# HIVNAT 001.2: Pharmacokinetics (PK) of Lower Doses of Saquinavir-Soft Gel Caps (SQV) (800 and 1200 mg bid) with Itraconazole (Itra) Compared to 1400 mg SQV bid without Itra in HIV-1+ Thai Patients

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## Abstract

**Objective:** Investigate the pharmacokinetics of 800 mg and 1200 mg Saquinavir-Soft-Gel-Caps (SQV-SGC) bid plus 100mg itraconazole od compared to 1400 mg SQV-SGC bid without itraconazole.

**Design:** 17 randomly selected patients on 1400 mg SQV-SGC plus AZT/3TC or d4T/ddl, were switched to 800 mg or 1200 mg SQV-SGC bid plus itraconazole 100 mg od. Steady-state SQV pharmacokinetics was determined on 1400mg bid SQV-SGC without itraconazole and after 2 weeks with the lower SQV-SGC doses plus itraconazole.

**Methods:** SQV plasma concentrations were determined just before, and at 11 more times over 12 hours after taking SQV-SGC by a sensitive/validated RP-HPLC methodology. Area under plasma concentration-versus-time curve (AUC), maximum (C<sub>max</sub>) and minimum (C<sub>min</sub>) concentration, time to C<sub>max</sub> (T<sub>max</sub>) and elimination half-life (t<sub>1/2</sub>) was calculated by a non-compartmental model.

**Results:** Median (IQR) steady-state SQV pharmacokinetic parameters:

|                                     | patients | AUC <sub>0-12h</sub> *mg/L | C <sub>max</sub> (mg/L) | T <sub>max</sub> (h) | C <sub>min</sub> (mg/L) | t <sub>1/2</sub> (h) |
|-------------------------------------|----------|----------------------------|-------------------------|----------------------|-------------------------|----------------------|
| SQV-SGC 1400 mg bid no itraconazole | 17       | 3.33<br>(1.96-7.34)        | 1.05<br>(0.69-2.48)     | 2.0<br>(1.8-3.0)     | 0.09<br>(0.04-0.13)     | 4.6<br>(4.0-6.0)     |
| SQV-SGC 1200 mg bid + itraconazole  | 9        | 4.29<br>(3.14-7.67)        | 1.42<br>(0.60-2.19)     | 2.0<br>(1.5-2.5)     | 0.11<br>(0.06-0.14)     | 5.0<br>(4-7.5)       |
| SQV-SGC 800 mg bid + itraconazole   | 8        | 4.07<br>(2.76-4.49)        | 0.98<br>(0.84-1.21)     | 2.6<br>(1.9-3.3)     | 0.08<br>(0.06-0.08)     | 5.1<br>(4.7-6.1)     |

**Conclusion:** SQV-SGC 800 mg or 1200 mg bid boosted with 100 mg itraconazole od resulted in adequate SQV pharmacokinetics equivalent to SQV-SGC 1400 mg bid, a benefit in developing countries with limited drug access/affordability.

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## Introduction

**Purpose:** Evaluate pharmacokinetics of low dose SQV-SGC bid (800 and 1200 mg ) plus 100 mg Itraconazole od compared to 1400 mg SQV-SGC bid without itraconazole in pretreated HIV-1 infected Thai population

**Pretreatment:** AZT/ddC for 66 weeks followed by SQV-SGC 1400 mg bid and AZT/ 3TC, or d4T/ddl for 2 years  
 0, 100, or 200 mg itraconazole od was added for the last 52 weeks of bid therapy

**Itraconazole Washout:** Itraconazole was stopped for two weeks in subset of 17 randomly selected patients

### Two Pharmacokinetic Evaluations:

**First Pharmacokinetic evaluation** was done on all 17 patients after itraconazole washout while taking un-boosted SQV-SGC 1400 mg bid and dual NRTI's  
 Patients then randomized to take either 800 mg or 1200 mg SQV-SGC bid plus 100 mg itraconazole od for two more weeks plus dual NRTI's

**Second Pharmacokinetic evaluation** on low dose boosted SQV-SGC

## Method

- PK curves were obtained from 17 randomly selected patients
- Steady State Pharmacokinetics of SQV:
  - Overnight fast
  - Blood samples: just before, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 hours after ingestion of SQV-SGC or SQV-SGC + itraconazole
  - Take ARV with a meal (10-15 g fat, 400-700 kcal)
  - RP-HPLC method (min. quantification of 25 ng/mL)
- Statistics: Wilcoxon Matched Pairs Signed Ranks test

### PK Outcome Variables:

- Area under the plasma concentration versus time Curve (AUC[0-12 h])
- Minimum concentration (C<sub>min</sub>)
- Maximum concentration (C<sub>max</sub>)
- Time to C<sub>max</sub> (T<sub>max</sub>)
- Elimination half-life (t<sub>1/2</sub>)

## Results

### Baseline Characteristics

|                     |                  |
|---------------------|------------------|
| Males/Females       | 5/12             |
| Median age (IQR)    | 32 years (28-36) |
| Median weight (IQR) | 51 kg (47-58)    |

Median (IQR) pharmacokinetic parameters of saquinavir as measured after simultaneous ingestion of saquinavir soft-gelatin capsules 1400 mg bid without itraconazole versus 800 or 1200 mg bid plus itraconazole 100 mg od in 17 HIV-1-infected patients, and the number of patients on un-boosted and boosted SQV with C<sub>min</sub> < 0.05 mg/L:

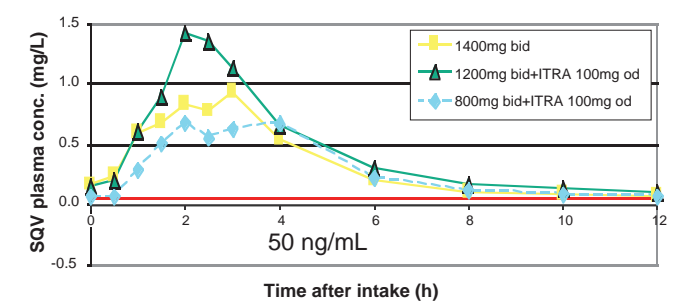
| SQV dose-bid  | patients | AUC <sub>0-12h</sub> *mg/L | C <sub>max</sub> (mg/L) | T <sub>max</sub> (h) | C <sub>min</sub> (mg/L) | t <sub>1/2</sub> (h) | # patient with C <sub>min</sub> < 0.05mg/L |
|---------------|----------|----------------------------|-------------------------|----------------------|-------------------------|----------------------|--|
| 1400 mg       | 17       | 3.33<br>(1.96-7.34)        | 1.05<br>(0.69-2.48)     | 2.0<br>(1.8-3.0)     | 0.09<br>(0.04-0.13)     | 4.6<br>(4.0-6.0)     | 5  |
| 1200 mg +itra | 9        | 4.29<br>(3.14-7.67)        | 1.42<br>(0.60-2.19)     | 2.0<br>(1.5-2.5)     | 0.11<br>(0.06-0.14)     | 5.0<br>(4.0-7.5)     | 1  |
| 800 mg +itra  | 8        | 4.07<br>(2.76-4.49)        | 0.98<br>(0.84-1.21)     | 2.6<br>(1.9-3.3)     | 0.08<br>(0.06-0.08)     | 5.1<br>(4.7-6.1)     | 1  |

AUC<sub>0-12h</sub> = area under the plasma concentration versus time curve from 0 to 12 h, C<sub>max</sub> = maximal concentration, C<sub>min</sub> = minimal concentration at 24 h post dose, t<sub>max</sub> = time to reach C<sub>max</sub>, t<sub>1/2</sub> = plasma elimination half-life.

### Geometric Mean Ratio's (GMR) plus 90 % Confidence Interval and P values

| Saquinavir-soft gel cap (SQV-SGC) dose | Parameter               | Geometric mean ratio and 90% CI | P-value |
|--|-------------------------|---------------------------------|---------|
| 800 mg bid+Itra vs 1400 mg bid         | AUC (h*mg/L)            | 0.82<br>(0.52-1.28)             | 0.43    |
|  | C <sub>min</sub> (mg/L) | 0.79<br>(0.57-1.09)             | 0.20    |
|  | C <sub>max</sub> (mg/L) | 0.71<br>(0.44-1.16)             | 0.22    |
| 1200 mg bid vs 1400 mg bid             | AUC (h*mg/L)            | 1.47<br>(0.79-2.75)             | 0.28    |
|  | C <sub>min</sub> (mg/L) | 1.27<br>(0.86-1.87)             | 0.28    |
|  | C <sub>max</sub> (mg/L) | 1.24<br>(0.78-1.99)             | 0.42    |

Steady-state SQV levels (SQV-SGC 1400 mg bid vs 1200 mg and 800 mg bid boosted with itraconazole 100 mg od, n=17): The red line represents the proposed critical threshold SQV concentration of 50 ng/mL



## Conclusion

- Pharmacokinetic data suggest that lower doses of SQV-SGC (800 or 1200 mg bid) boosted with 100 mg itraconazole once-daily resulted in adequate SQV PK parameters not significantly different from SQV-SGC 1400 mg bid
- SQV-SGC 800 mg bid boosted with 100 mg itraconazole once-daily may be a more convenient regimen that has lower costs and pill burden (9 pills vs 14 pills) than SQV-SGC 1400 mg bid
- Even lower SQV-SGC doses may be possible with itraconazole or other boosting agents such as ritonavir (RTV)
- Adequate PK parameters were found with SQV-SGC/RTV 1600/100 mg od, but the cost of RTV 100 mg is US\$ 0.82/cap while itraconazole is US\$ 0.44/cap. The SQV AUC<sub>0-24h</sub> was higher when boosted with RTV vs. itraconazole (35.5 vs 8.1 h\*mg/L).

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