Antiretroviral therapy in Thai adults and children with HIV-1 infection
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CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: results of the Staccato randomised trial

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CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: results of the Staccato randomised trial

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Summary
Background Stopping antiretroviral therapy in patients with HIV-1 infection can reduce costs and side-effects, but carries the risk of increased immune suppression and emergence of resistance.

Methods 430 patients with CD4-positive T-lymphocyte (CD4) counts greater than 350 cells per μL and viral load less than 50 copies per mL were randomised to continued therapy (n=146) or scheduled treatment interruptions (n=284). Median time on randomised treatment was 21.9 months (range 16.4–25.3). Primary endpoints were proportion of patients with viral load less than 50 copies per mL at the end of the trial, and amount of drugs used. Analysis was intention-to-treat. This study is registered at ClinicalTrials.gov with the identifier NCT00113126.

Findings Drug savings in the scheduled treatment interruption group, compared with continuous treatment, amounted to 61.5%. 257 of 284 (90.5%) patients in the scheduled treatment interruption group reached a viral load less than 50 copies per mL, compared with 134 of 146 (91.8%) in the continued treatment group (difference 1.3%, 95% CI 4.3 to 6.9, p=0.8). No AIDS-defining events occurred. Diarrhoea and neuropathy were more frequent with continuous treatment; candidiasis was more frequent with scheduled treatment interruption. Ten patients (2%) had resistance mutations, with no significant differences between groups.

Interpretation Drug savings with scheduled treatment interruption were substantial, and no evidence of increased treatment resistance emerged. Treatment-related adverse events were more frequent with continuous treatment, but low CD4 counts and minor manifestations of HIV infection were more frequent with scheduled treatment interruption.

Introduction Although the introduction of highly active antiretroviral therapy (HAART) has improved AIDS-free survival, treatment can lead to acute and progressive side-effects1 and costs can limit the affordability of drugs.2 By decreasing the time that patients receive medications, intermittent HAART could reduce toxic effects and cost of long-term treatment.3 However, stopping HAART increases the risk of clinical disease progression if CD4-positive T-lymphocyte (CD4) counts fall and drug resistance can emerge due to persistence of residual drug concentrations after stopping drug.4 The Staccato study was originally designed to assess CD4-guided and fixed-cycle week-on-week-off strategies compared with continuous treatment. However, an interim analysis showed an unacceptably high rate of failure in the week on, week off group. This arm was therefore discontinued.5 We present the results of the comparison between the CD4-guided scheduled treatment interruptions and continuous treatment strategies.

Methods Setting and study population Staccato was a prospective, open-label, randomised, multicentre trial done in Thailand, Switzerland, and Australia. We recruited patients with chronic HIV-1 infection and virological and immunological response to HAART. Inclusion criteria were CD4 count greater than 350 cells per μL and HIV-1 RNA less than 50 copies per mL for at least 3 months before screening, and no evidence for pre-existing drug resistance, such as detectable viral load during previous antiretroviral therapy.

Randomisation was stratified by country and by pre-treatment concentrations of HIV-1 RNA <100 000 vs ≥100 000 copies per mL using the random number generator of SPSS 11.0 (SPSS, Chicago, IL, USA), and a system of closed envelopes. Patients were randomised in 1:2 proportion to receive continuous HAART, or CD4-guided treatment interruptions. Patients were enrolled and assigned to groups by the study nurses in Switzerland (MLB) and Thailand (TI), and by the medical study coordinator (JC) in Australia.

Procedures In Thailand, HAART consisted of two nucleoside reverse transcriptase inhibitors (NRTIs) plus saquinavir-ritonavir 1500 mg or 1600 mg/100 mg once daily. NRTIs for Thai patients were initially stavudine and didanosine, replaced by tenofovir and lamivudine in

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March, 2003, and by tenofovir and emtricitabine in September, 2004. The 84 patients in Switzerland and Australia received a range of HAART regimens. Treatment changes for perceived toxic effects or inefficacy were allowed, as dictated by good clinical practice (see also webtable 1). Patients were assessed for CD4 count, viral load (Roche Amplipcr Ultra-sensitive assay Palo Alto, USA), complete blood-cell counts, clinical chemistry, clinical and laboratory adverse events, and HIV disease progression every 4 weeks over the first 12 weeks, and every 12 weeks thereafter. Lipodystrophy was scored by a questionnaire, filled out by a study doctor who interviewed the patients every 24 weeks.

In the scheduled treatment interruption group, patients started the trial by discontinuing HAART, with no-nucleosides (NNRTIs) being discontinued 1 week before the other drugs. If the CD4 count dropped below 350 cells per µL, a second sample was drawn immediately; if the CD4 count of the second sample was again below 350 cells per µL, patients re-started HAART for at least 12 weeks. They stopped again if the confirmed CD4 count rose above 350 cells per µL.

Randomised treatment continued until a scheduled visit occurred between February and April, 2005. Thereafter, all patients were given continuous HAART for 12 weeks. Patients with viral load less than 50 per mL then left the trial. Patients with a viral load greater than 50 copies per mL were treated for a further 12 weeks and re-assessed.

The primary endpoints were the proportion of patients with viral load less than 50 copies per mL at the end of the trial, and the amount of drugs used in the scheduled treatment interruption group, compared with the continued treatment group.

We used two complementary methods to measure drug savings. In the start-at-randomisation method, days on drug were counted from the day of randomisation until the end of randomised treatment, and compared between the two groups for all patients. In a subgroup of 187 Thai patients who started HAART with the intention of randomising later to scheduled treatment interruption or continued treatment, the start-at-HAART method was also used. The days on drug were counted from the first day on HAART until the end of randomised treatment. Secondary endpoints included CD4 count, occurrence of drug resistance mutations, and drug-related and HIV-related adverse events.

We planned to enrol 200 patients in the continuous treatment group and 400 patients in the scheduled treatment interruption group. This sample size would have yielded a power of 90% to detect a difference in proportions of patients who achieved the primary endpoint (viral load <50 copies per mL) of 10% vs 20%, with type 1 error of 0.05.7 The effective power with the enrolled sample size (145+284) was 80%.

## Statistical analysis

Analyses were intention-to-treat. Comparisons of proportions were based on the χ² test, and comparisons of quantitative variables on Student’s t test or Mann-Whitney test, as appropriate.8

The probability of re-initiation of HAART after stopping in the scheduled treatment interruption group was assessed with a multivariate Cox proportional-hazards model, after adjustment on covariates that showed significant differences in the univariate analysis.7 Factors associated with the probability of re-starting HAART in the scheduled treatment interruption group were analysed with univariate and multivariate Cox proportional-hazards models. The covariates analysed in the model were: sex, route of infection (transmission by homosexual or bisexual sex, heterosexual sex, intravenous drug use, or other), US Centers for Disease Control and Prevention (CDC) stage at baseline, centre (Switzerland, Thailand, or Australia), age at baseline (groups defined by quartiles: <17 to ≤<30, ≥30 to <35, ≥35 to <41, and ≥41 years), CD4 count before HAART (quartiles 2–209, 209–268, 268–339, >339 cells per µL), viral load before HAART (1–0–4–28, 4–28–4–71, 4–71–5–2, >5–2 copies per mL), and CD4 count at screening (350–408, 408–485, 485–605, >605 cells per µL). The assumption of proportional hazards was ascertained by visual inspection of survival functions. All variables associated with re-initiation of HAART in the scheduled treatment interruption group at p<0–1 in univariate analysis were included in the final multivariate model.

To assess the proportion with viral load less than 50 copies per mL, the viral load of patients in the scheduled treatment interruption group was measured after the 12 or 24 weeks of continuous re-treatment received by all these patients between the end of 2004 and the summer of 2005. In the continuous treatment group, the first viral load measurement between May and October, 2005, was used. For patients who no longer followed the Staccato protocol but were followed up after exclusion, an attempt was made to obtain a viral load measurement during the same period; if a measurement could not be obtained, a sensitivity analysis was done. We compared the last observation carried forward method with the missing—failure method. We present the results from the method that was less favourable to the intervention (scheduled treatment interruption). We assessed the difference of the proportion of virological success (ie, viral load <50 copies per mL) with the asymptotic χ² test. All other analyses were done with SPSS 11.0 (SPSS, Chicago, IL, USA).

This study is registered at ClinicalTrials.gov with the identifier NCT00113126.

### Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
Results
548 patients were recruited (439 [80-2%] in Thailand, 100 [18-2%] in Switzerland, and nine [1.6%] in Australia), including 285 treatment-naive Thai patients with CD4 counts of 200–350 cells per μL, who started HAART with the intention to enrol in Staccato as soon as randomisation criteria were met (figure 1).

Patients were recruited between October, 2001, and December, 2004. They were followed up from October, 2001, to November, 2005, depending on centres and time of recruitment.

Baseline characteristics were well balanced between the treatment groups (table 1). There were 198 men (46-0%) and 232 women (54-0%), with mean age 36-8 years (median 35-5; range 17-70) and most patients were either in CDC stage A (259 patients, 60-2%) or B (132, 30-7%). Mean duration of antiretroviral treatment before the trial was 23-7 months (median 15 months, range 6-93).

Participants spent a total of 746 patient-years on randomised treatment (mean 1-73 years per patient, median 1-82, range 0-07–3-55); 484 patient-years for scheduled treatment interruption and 262 patient-years on continuous therapy. In 19 instances, treatment was continued although the protocol would have required interruption, and in seven instances scheduled treatment interruption was continued although the protocol would have required re-starting treatment, compared with 2321 instances in which treatment decisions were made according to protocol. 44 patients in the continued treatment group, and 46 patients in the scheduled treatment interruption group, had major protocol violations, defined as missing two consecutive visits or prolonged non-adherence to assigned treatment. Viral load status at the end of the trial was available for 44 of these 60 patients; 16 were lost to follow-up (3-7%; 12 scheduled treatment interruption, four continued treatment).

Figure 2 shows the probability of re-treatment in the scheduled treatment interruption group during Staccato. 50% (7/14) of patients restarted HAART within 18 weeks of randomisation. After 100 weeks, 75% (117) of patients had been treated again. Results of unadjusted and adjusted Cox regression analyses are presented in table 2. The predictors of HAART associated with re-starting HAART in the scheduled treatment interruption group were a lower CD4 count before HAART initiation, lower CD4 count at Staccato screening, higher viral load before starting HAART, after adjustment for all covariates with p<0.10 in univariate analyses.

At the end of randomised treatment (and before the 12 weeks continuous re-treatment for the scheduled treatment interruption group), mean CD4 counts were 402 cells per μL (median 374, range 302–1037) in the scheduled treatment interruption group, and 619 cells per μL (601, 178–1295) in the continued treatment group (p=0.001, Student’s t test; webfigure). In the scheduled treatment interruption group, 147 patients (60-5%) had a CD4 count greater than 150 cells per μL compared with 127 (96-2%) in the continuous treatment group (p=0.001).

After the 12 weeks of re-treatment received by all patients prior to the end of the study, the mean CD4 count rose in the scheduled treatment interruption group from 402 to 484 cells per μL (median 459, range 233–1680), but remained below that of the continued treatment group: 655 cells per μL (608, 319–1622; p=0.001; webfigure). The rise in CD4 count during re-treatment was more rapid than after initiation of HAART.26

When the start at randomisation method was used for calculation, patients in the scheduled treatment interruption group had consumed drugs during 37-5%
of days, compared with 99% of days in the continued treatment group, resulting in a saving of 61.5%. Using the start at HAART method in the 187 HAART-naive Thai patients who started treatment with the intention of enrolling in Staccato, drug savings amounted to 31.2%. Figure 3 shows drug savings as a function of time, calculated with either method. 32 patients (22 of 284 [7.7%]) in the continued treatment group and ten of 146 (6.8%) in the scheduled treatment interruption arm, p=0.74) had a viral load greater than 500 copies per mL after having supposedly taken at least 12 weeks of continuous HAART. Voluntary interruptions of treatment, or other problems related to adherence, were strongly suspected in 23 of these patients (17 in the continued treatment group, six in the scheduled treatment interruption group).

240 patients in the scheduled treatment interruption group were re-treated at the end of the study. 224 of these patients (93.3%, 95% CI 90.2–96.9) reached a viral load less than 50 copies per mL within 24 weeks. We attempted to follow up all patients, including those with protocol violations, and assess their viral load at the end of the study. 16 patients (7–7%) were lost to follow-up, and their last observation was carried forward. In the scheduled treatment interruption group, 257 of 284 (90.5%) had a viral load less than 50 copies, compared with 134 of 146 (91.8%) in the continued treatment group. The difference of 1.3% (95% CI 4.3–6.9%) between the groups was not significant (p=0.90). Sequencing of HIV reverse transcriptase and protease genes was attempted when resistance was suspected because of detectable viral load despite treatment (ten patients in scheduled treatment interruption group and 22 on continuous treatment). Additionally, the viral genomes from all 126 patients who underwent at least two stop-start cycles in the scheduled treatment interruption group were also sequenced. 156 patients satisfied the criteria for sequencing. For nine, a sample was not available, and for 13, amplification was not successful; genotypic resistance analysis was completed in 133 patients.

Table 2: Cox model for time to re-start HAART in scheduled treatment interruption group (n=243) by predictor

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 (cells per µL) at screening&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50&lt;50</td>
<td>55</td>
<td>1.00</td>
</tr>
<tr>
<td>50–490</td>
<td>65</td>
<td>0.63 (0.44–0.90)</td>
</tr>
<tr>
<td>491–450</td>
<td>57</td>
<td>0.43 (0.29–0.65)</td>
</tr>
<tr>
<td>&gt;450</td>
<td>66</td>
<td>0.14 (0.09–0.22)</td>
</tr>
<tr>
<td>CD4 (cells per µL) before ART&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–209</td>
<td>58</td>
<td>1.00</td>
</tr>
<tr>
<td>210–268</td>
<td>58</td>
<td>0.75 (0.52–1.08)</td>
</tr>
<tr>
<td>&gt;268</td>
<td>61</td>
<td>0.21 (0.10–0.45)</td>
</tr>
<tr>
<td>&gt;335</td>
<td>66</td>
<td>0.10 (0.06–0.16)</td>
</tr>
<tr>
<td>Viral load (log&lt;sub&gt;10&lt;/sub&gt; copies per mL) before ART&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>59</td>
<td>1.00</td>
</tr>
<tr>
<td>4–4.7</td>
<td>62</td>
<td>1.64 (1.06–2.55)</td>
</tr>
<tr>
<td>4.7–5.2</td>
<td>60</td>
<td>1.56 (1.03–2.37)</td>
</tr>
<tr>
<td>&gt;5.2</td>
<td>62</td>
<td>2.02 (1.33–3.11)</td>
</tr>
<tr>
<td>Route of HIV-1 infection&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual transmission</td>
<td>188</td>
<td>1.00</td>
</tr>
<tr>
<td>Heterosexual/bisexual transmission</td>
<td>42</td>
<td>0.61 (0.40–0.91)</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>4</td>
<td>1.87 (0.53–6.65)</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>1.10 (0.26–4.36)</td>
</tr>
<tr>
<td>CDC stage at screening&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>148</td>
<td>1.00</td>
</tr>
<tr>
<td>B</td>
<td>78</td>
<td>1.85 (1.27–2.60)</td>
</tr>
<tr>
<td>C</td>
<td>17</td>
<td>2.50 (1.13–5.41)</td>
</tr>
</tbody>
</table>

ART=antiretroviral therapy; HR=hazard ratio. *p<0.01; †p<0.001.

Figure 2: Probability of re-starting treatment in the scheduled treatment interruption group.

Figure 3: Proportion (%) of drugs saved by use of scheduled treatment interruption depending on two methods of calculation.
resistance, compared with treatment with ritonavir-boosted saquinavir, was 14.9% (95% CI 3.02–74.08) for HAART containing three NRTIs (p=0.01).

Table 3 lists adverse events that were reported with a frequency of more than 2% in either group. During the first scheduled treatment interruption, 17 patients (5.9%) experienced symptoms, such as fever, sore throat, or skin lesions, indicative of acute retroviral syndrome, but only six of these had a viral load of more than 10^6 copies per mL. These symptoms were not detected prospectively during the trial. Diarrhoea and neuropathy were more frequent in the continued treatment group, whereas oral or genital candidiasis and thrombocytopenia were more in the scheduled treatment interruption group. The cumulative incidence of neuropathy was 2.3 per 100 with scheduled treatment interruption, and 4.58 per 100 person-years with continued treatment (p=0.03, log-rank test). The incidence of neuropathy was 19.3 per 100 person-years of observation on didanosine-stavudine, but only 1.8 per 100 on tenofovir-lamivudine (p<0.0001).

One patient died in the continued treatment group due to stroke, and one died in the scheduled treatment interruption group from colon cancer; neither death was related to HIV or study drugs. No new AIDS-defining events occurred.

Concentrations of total cholesterol and LDL cholesterol were lower in the scheduled treatment interruptions group (by 0.7–3.0 4 mmol/L, p=0.001), and this difference tended to disappear when all patients were receiving HAART at the end of the study (webtable 2).

Arrandomisation, a slightly greater proportion of patients had self-reported lipodystrophy in the continued treatment group (12.0%, 17 of 144) than in the scheduled treatment interruption group (10.2%, 28 of 278, p=0.07). The prevalences of lipodystrophy were 8.6% (23 of 268) in the scheduled treatment interruption group and 12.5% (17 of 134) in the continued treatment group at 24 weeks (p=0.0001), 10.0% versus 15.1% (p=0.0001) at 48 weeks, and 7.9% versus 13.4% (p=0.0001) after 72 weeks.

Discussion

We compared a CD4-guided scheduled treatment interruption strategy with continuous HAART in a prospective, randomised trial. Virological responses in the scheduled treatment interruption group, who were all given at least 12 weeks of continuous re-treatment before the end of the trial, were very similar to those in the continued treatment group, and we did not find a significant difference in drug resistance between the groups. Our calculations of the amount of medication used by each group showed that the potential for diminishing use of antiretroviral drugs through scheduled treatment interruptions is substantial.

The scheduled treatment interruption group had a higher incidence of oral and genital candidiasis, presumably because of their lower CD4 counts. Incidence of symptoms of acute retroviral syndrome was low in the

<table>
<thead>
<tr>
<th>Drug-related adverse events</th>
<th>Scheduled treatment interruption</th>
<th>Continuous therapy</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>44 (15.5%)</td>
<td>15 (10.3%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>45 (15.8%)</td>
<td>34 (23.3%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

HIV-related adverse events

Acute retroviral syndromea: 17 (5.9%), of which 6 (2.3%) with high viral loadb

Oral or genital candidiasis: 11 (3.9%) (p=0.07)

Thrombocytopenia (platelets <100 G/L): 7 (2.3%) (p=0.12)

Other adverse events

Neuropathy: 11 (3.9%) (p<0.0001)

Table 3: Number (%) of patients with adverse events during randomised treatment phase


Like all studies of treatment interruption reported so far, Staccato did not use dummy drugs to mask patients’ treatment status. Among the disadvantages of the open design is the difficulty to ascribe adverse events to either HIV or drugs. The same difficulty also applies to the measurement of lipodystrophy. Reported rates of lipodystrophy decreased in the scheduled treatment interruption group, but not in the continued treatment group, between the time of randomisation, 24 weeks, and 48 weeks. This change might indicate an advantage of scheduled treatment interruptions, but is difficult to interpret in the absence of objective evidence about the distribution of fatty tissue, such as continued treatment or dual energy x-ray absorptiometry scans.

Although peer-reviewed published work in this area is sparse, treatment interruption studies presented at conferences have emphasised the worrisome frequency of acute retroviral syndromea and resistance mutations. Our results are in marked contrast, and it is worth questioning these differences. The low incidence of acute retroviral syndrome in Staccato might be due to the relatively short
period between start of HAART and treatment interruption. Acute retroviral syndrome might occur because of waning anti-HIV immunity during the period of HAART before scheduled treatment interruption. If this is indeed the explanation, patients in Staccato, with less time on HAART preceding scheduled treatment interruption than patients in previous studies, were less at risk of acute retroviral syndrome. A low incidence of acute retroviral syndromes was also noted in another study where scheduled treatment interruption occurred after a relatively short period of HAART. The SMART study was interrupted because the incidence of AIDS-defining opportunistic infections or deaths reached 1.2 per 100 patient-years of follow-up in the scheduled treatment interruption group, compared with 1.5 in the continued treatment group. Staccato was not powered to discover differences in clinical endpoints, but the incidence rates seen in SMART would have produced about 17 AIDS-defining opportunistic events or deaths in Staccato’s scheduled treatment interruption group, whereas no AIDS-defining event and only one death were actually observed. Such a striking discrepancy is unlikely to be due to chance and requires explanation.

Most endpoints in SMART occurred at low CD4 counts; re-starting treatment at 350 cells per µl as in Staccato, rather than at 250 cells per µl as in SMART, would diminish the time spent with low CD4 counts and potentially abolish the differences between continued treatment and scheduled treatment interruption groups. Subgroup analyses of the SMART population suggest, however, that some difference between the groups persisted even at high CD4 counts. The time spent on HAART before scheduled treatment interruption (median of 16 months in Staccato, and 72 months in SMART), and the type of HAART used, also differed between Staccato and SMART, but the relation between those differences, and the apparently different outcome, is not obvious.

It would be wrong to conclude that SMART means the end of all HIV treatment interruptions. Among the millions of patients who take HAART, hundreds of thousands will stop treatment, because some will not be able to tolerate the pills, whereas others will consider SMART’s results (depending on the CD4 count, 0–5 = 3 excess events avoided per 100 patient-years of treatment) and decide for themselves that the benefits are not worth the inconvenience of continued treatment. In Switzerland, less than 40% of the patients in SMART’s treatment interruption group, who were all extensively counselled about the results of the trial, have started treatment again so far.

For these patients, Staccato’s results provide reassurance about the one risk that was widely feared when these trials began—development of resistance and loss of efficacy of treatment. Staccato indicates that ritonavir-boosted protease-inhibitor-based HAART can be interrupted without undue harm, provided that CD4 counts are monitored. Emergence of resistance to treatment is so rare that monitoring of viral load might not be necessary. The absence of AIDS-defining opportunistic diseases suggests that with CD4 criteria differing from those of SMART, the safety of treatment interruption could be enhanced. Scheduled treatment interruptions lasting many months, with substantial savings, can be anticipated if CD4 counts, at the time of interruption, exceed 500 cells per µl, especially in patients who had never been severely immunosuppressed.

The Staccato Study Group

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B. Hirschel and H. J Furrer had the idea for the study and wrote the protocol together with J Ananworanich, K Baurangphas, P Phanuphak, D Cooper, and A Hill. Gayet-Ageron analysed the results, supervised by T Permpeng J Ananworanich organised the study in Thailand, with help from M Le Brat, who monitored the study in all centres. S Yerli, L. Pernin, and S Tricharakul defined the strategy for resistance testing and analysed all samples. W. Pratthatchai, C. Chantarakam, G. Kiertibut, W. Pramathanak, P. Rakasukal, T. Sonnprasamud, M. Carassius, U. Karrer, D. Germain, R. Nuesch, P. Vernazza, E. Bernasconi, D. Ledue, and C. Suchet were responsible for patients’ inclusion and follow-up during
the study. B Hirschfeld drafted the present paper and finalized it with input from J Ananworanich, H Parret, A Gayet-Ageron, and D Gosport. All contributors contributed to and approved the final version of the manuscript.

Conflict of interest statement
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