

## TMC125 exerts similar initial antiviral potency as a five-drug, triple class antiretroviral regimen

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**Objective:** TMC125, a next generation, non-nucleoside reverse transcriptase inhibitor (NNRTI), demonstrated a remarkable decline of plasma HIV-1 RNA during a phase IIa study. We compared the initial rate of decline of plasma HIV-1 RNA achieved by TMC125 monotherapy with that of a triple class, five-drug regimen, containing drugs from all three currently licensed classes (zidovudine, lamivudine, abacavir, indinavir and nevirapine).

**Methods:** The decline in plasma HIV-1 RNA of 12 HIV-1 infected, antiretroviral (ART) naive patients treated for 1 week with TMC125 monotherapy was compared with that observed in the ERA study ( $n = 11$ ). The plasma HIV-1 RNA elimination rate constant was calculated based on at least four plasma HIV-1 RNA measurements during the first week of treatment (first-order elimination) and compared using the Student's *t* test.

**Results:** Median ages were 23 and 38 years for TMC125 and ERA patients, respectively ( $P = 0.001$ ), median baseline plasma HIV-1 RNA levels were 4.2 and 4.8  $\log_{10}$  copies/ml ( $P = 0.001$ ) and median baseline CD4 T-cell counts were  $458 \times 10^6$  and  $360 \times 10^6$  cells/l ( $P = 0.08$ ). The median plasma HIV-1 RNA elimination rate constant was 0.68/day in TMC125 treated patients, and 0.56/day in ERA participants ( $P = 0.24$ ). The median decline in plasma HIV-1 RNA after 7 days was 1.92 and 1.76  $\log_{10}$  copies ( $P = 0.77$ ) and the median increase of CD4 T cells was  $119 \times 10^6$  and  $60 \times 10^6$  cells/l, respectively ( $P = 0.29$ ).

**Conclusion:** Monotherapy with TMC125 in ART-naive, HIV-1-infected individuals resulted in a similar rate of decline of plasma HIV-1 RNA during 1 week of therapy as therapy with a five-drug regimen.

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*AIDS* 2003, **17**:2623–2627

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Note: Part of this study was presented at the *Ninth Conference on Retroviruses and Opportunistic Infections*. Seattle, February 2002.

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Received: 5 December 2002; revised: 28 February 2003; accepted: 7 May 2003.

DOI: 10.1097/01.aids.0000096860.36052.03

**Keywords: TMC125, non-nucleoside reverse transcriptase inhibitors, viral dynamics**

## Introduction

Despite the dramatically improved clinical outlook for HIV-1 patients with current antiretroviral therapy (ART) [1-4] eradication of HIV is not possible because of ongoing low-level replication and the presence of latently infected, resting CD4 T cells harbouring replication-competent HIV-1 [5-8]. Experimental attempts to lower the pool of latently infected resting CD4 T cells with OKT3 were unsuccessful [9,10], probably because of the ongoing low level of replication.

The incidence and prevalence of drug-resistant viruses is increasing. This makes the development of new, potent antiretroviral drugs with activity against wild-type and drug resistant viruses a necessity. One such new drug is the non-nucleoside reverse transcriptase inhibitor (NNRTI) TMC125, which is a diarylpyrimidine derivative. *In vitro*, TMC125 has a high potency against wild-type HIV-1 [50% effective concentration ( $EC_{50}$ ), 1 nM] and key single and double mutants resistant to current NNRTI.

A phase IIa study with TMC125 in treatment-naive individuals demonstrated a very rapid decline of plasma HIV-1 RNA during 1 week of monotherapy, resulting in an average decrease in viral load of nearly  $2 \log_{10}$  [11]. This compares favourably to a recent study by Louie *et al.* [12], in which a highly potent regimen (efavirenz, lopinavir/ritonavir, lamivudine and abacavir) reduced the plasma HIV-1 RNA within 7 days by  $1.59 \log_{10}$  on average. These authors concluded that 1 week of treatment is sufficient to evaluate the potency of an antiretroviral regimen, and that a completely efficacious regimen would lead to reductions in viral load of  $1.59 \log_{10}$  and above, rather than the viral load drops of  $1.32 \log_{10}$  reported for standard triple antiretroviral regimens.

We have previously reported the same conclusion in a study in which we compared a ritonavir-based triple therapy with a five-drug regimen (ERA study) in treatment-naive HIV-1 infected patients [13]. The five-drug regimen resulted in a significantly higher rate of plasma HIV-1 RNA decline than the triple therapy.

In the current study, we retrospectively compared the rate of decline of plasma HIV-1 RNA after 1 week of TMC125 monotherapy in treatment-naive subjects with the rate of decline during the first week of treatment with this five-drug containing regimen (ERA study) [13]. We also retrospectively compared the TMC125 data with data obtained during a standard triple antiretroviral regimen [14,15].

## Methods

### Patients

Data were obtained from two studies. The first study, TMC125-C208, was a Phase IIa randomized, double-blind, placebo-controlled study, performed in 2001 at the Infectious Diseases Hospital, Moscow and the Medical Academy of Postgraduate Studies, Department of Infectious Diseases, St. Petersburg, in the Russian Federation. The aim of the trial was to assess the antiviral activity, tolerability, safety, viral resistance and pharmacokinetics of TMC125 during a 7-day monotherapy in ART-naive subjects with HIV-1 infection [11]. TMC125 was administered orally to 12 patients in a dosage of 900 mg twice daily. The treatment duration was limited to 7 days to prevent the selection of NNRTI-resistant mutants since a rapid emergence of resistance has been observed for first-generation NNRTI when given as monotherapy [16].

The second study, the ERA study, was a study performed at the Academic Medical Center of the University of Amsterdam, The Netherlands between 1997 and 2000. This study evaluated the effect of a five-drug, triple-class antiretroviral regimen in ART-naive patients with either a primary or a chronic HIV-1 infection [13]. Since patients with a primary infection have a slower plasma HIV-1 RNA decline after start of treatment [17], they were excluded from the present analysis. Eleven ART-naive patients with a chronic HIV-1 infection started with five drugs from all three classes of currently available antiretroviral drugs: zidovudine 300 mg twice daily, lamivudine 150 mg twice daily, abacavir 300 mg twice daily, indinavir 1000 mg three times daily and nevirapine 200 mg once daily during the first 2 weeks and then 400 mg daily. One patient started with stavudine 40 mg twice daily instead of zidovudine.

### HIV-1 RNA quantification

Plasma HIV-1 RNA levels in participants of the TMC125 study were measured with the Roche Amplicor HIV-1 Monitor test (version 1.5; Roche Diagnostics, Almere, The Netherlands) with a lower limit of quantification (LLQ) of 50 copies/ml. In the ERA study, plasma HIV-1 RNA levels were measured using the NucliSens HIV-1 QT assay (Organon Teknika, Boxtel, The Netherlands) with a lower limit of quantification (LLQ) of 50 copies/ml.

### Statistical analysis

The plasma HIV-1 RNA elimination rate constant (first order elimination) in the first week was calculated for all patients based on at least four measurements. HIV-1 RNA copies in plasma were measured every

12 h for 8 days in the TMC125 treated patients, and on day 0, 1, 3, 4 and 7 in the ERA patients (in two patients samples were taken at day 8 instead of day 7). We used an exponential function to describe the rate of plasma HIV-1 RNA decline during the first week for each patient, as we did in a previous study [13], using the following equation:  $V_t = V_0 \times e^{(-k \cdot t)}$  where the number of HIV-1 RNA copies per ml plasma at time  $t$  is represented by  $V_t$ , and at baseline by  $V_0$ ,  $k$  is the plasma HIV-1 RNA elimination rate constant per day, and  $t$  is the time (days) after the start of treatment. The half-life elimination of plasma HIV-1 RNA was calculated as follows:  $T_{1/2} = \ln 2/k$ .

Baseline characteristics and the plasma HIV-1 RNA elimination rate constants of the two treatment arms were compared using a Student's  $t$ -test.

In a separate analysis, the plasma HIV-1 RNA elimination rate in the first 7 days of treatment was compared between patients in the TMC125 study and patients on a triple regimen in the NUCB2019 study ( $n = 15$ ) [14,15], treated with zidovudine (300 mg twice daily), lamivudine (150 mg twice daily) and ritonavir (600 mg twice daily; started at 300 mg twice daily and escalated to full dose in 4 days).

## Results

Twelve patients received TMC125 monotherapy and 11 patients were treated in the ERA study. At baseline median ages were 23 and 38 years, respectively ( $P = 0.001$ ) and median plasma HIV-1 RNA levels

were 4.2 and 4.8  $\log_{10}$  copies/ml ( $P = 0.001$ ). Median CD4 T-cell counts were 458 and  $360 \times 10^6$  cells/l, respectively ( $P = 0.08$ ; Table 1). At day 7 all patients in both groups still had a detectable HIV-1 RNA in plasma.

The median plasma HIV-1 RNA elimination rate constant  $k$  was 0.68/day [interquartile range (IQR), 0.56–0.82] in TMC125-treated patients, and 0.56/day (IQR, 0.48–0.81) in ERA participants ( $P = 0.24$ ; Table 2). The median decline in HIV-1 RNA between day 0 and 7 was 1.92 and 1.76  $\log_{10}$  copies/ml, respectively ( $P = 0.77$ ; Fig. 1). Using only HIV-1 RNA measurements taken at the same time points as in the ERA group (day 0, 1, 3, 4 and 7), the median elimination rate constant in the TMC125 group remained similar (0.67 day<sup>-1</sup>; IQR, 0.52–0.80). The median increases of CD4 T cells after 1 week of therapy were 119 and  $60 \times 10^6$  cells/l, respectively ( $P = 0.29$ ).

In a separate analysis, the plasma HIV-1 RNA elimination rate constant during the first 7 days of treatment was calculated for the participants of the NUCB2019 study [14,15]. The median plasma HIV-1 elimination rate constant of 0.47/day (IQR, 0.35–0.57) was significantly lower than in patients who received TMC125 ( $P < 0.001$ ).

## Discussion

One week monotherapy with TMC125 in ART-naïve HIV-1 infected individuals resulted in a similar rate of

**Table 1. Baseline characteristics of the study patients.**

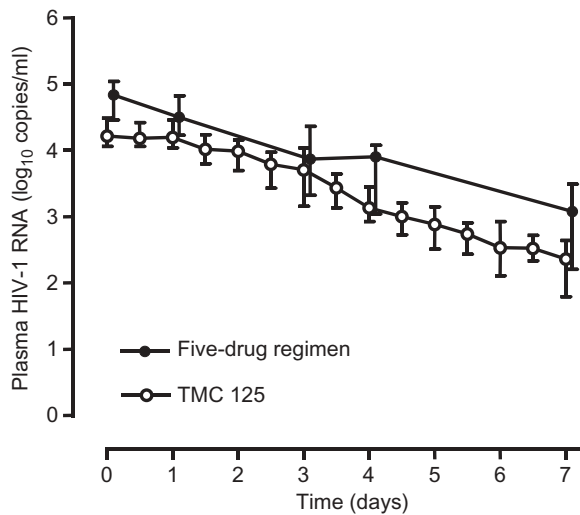
	TMC125-C208	Five-drug regimen (ERA)	$P^a$
Patients (n)	12	11	
Male [n (%)]	12 (100%)	11 (100%)	
Age (years) [median (SD)]	23 (9)	38 (8)	0.001
Plasma HIV-1 RNA			
Copies/ml [median (IQR)]	16602 (11496–30814)	69000 (29000–110000)	0.001
$\log_{10}$ copies/ml [median (IQR)]	4.2 (4.1–4.5)	4.8 (4.6–5.1)	
CD4 T cells count ( $\times 10^6/l$ ) [median (IQR)]	458 (341–625)	360 (110–520)	0.08

<sup>a</sup>Student's  $t$  test. SD, Standard deviation; IQR, interquartile range.

**Table 2. Virological and immunological results after 7 days of therapy.**

	TMC125-C208	Five-drug regimen (ERA)	$P^a$
Median plasma HIV-1 RNA decline ( $\log_{10}$ copies/ml)	1.92	1.76	0.77
Plasma HIV-1 elimination rate constant $k$ per day [median (IQR)]	0.68 (0.56–0.82)	0.56 (0.48–0.81)	0.24
Half-life of plasma HIV-1 RNA (days) [median (IQR)]	1.03 (0.85–1.25)	1.24 (0.86–1.45)	0.24
Median increase in CD4 T-cell count ( $\times 10^6/l$ )	119	60	0.29

<sup>a</sup>Student's  $t$  test.



**Fig. 1. Median plasma HIV-1 RNA during treatment.** Bars represent IQR.

decline of plasma HIV-1 RNA as that of a five-drug regimen during the first week of therapy.

In an earlier study we demonstrated that this five-drug regimen, containing drugs from all three currently available drug classes, provided a faster decline of plasma HIV-1 RNA after the start of treatment than therapy with a standard triple regimen [13]. Likewise, TMC125 monotherapy resulted in a significantly faster decline of plasma HIV-1 RNA than this standard triple regimen.

The patients in the TMC125 group were younger, but this does not correlate with long-term suppression of HIV-1 RNA plasma concentrations [18]. They also had a lower baseline HIV-1 RNA plasma level. It has been suggested that a higher baseline plasma HIV-1 RNA correlates with a faster first phase decay [19]. However, in that study, the patients with a higher baseline plasma HIV-1 RNA started with a triple therapy whereas the group with a lower baseline plasma HIV-1 RNA started with monotherapy and, after 3 weeks, switched to a triple therapy. The reported difference in decay rate is therefore more likely a result of the difference in potency between the two regimens than of the baseline plasma HIV-1 RNA [20]. Another study also showed that the baseline plasma HIV-1 RNA does not seem to have any effect on the plasma HIV-1 RNA elimination rate [21]. The assays used for the quantification of plasma HIV-1 RNA differed for the two studies, but the results of these assays are comparable, so it is unlikely that this affected the results [22].

TMC125 is designed to tightly and efficiently bind in the apolar pocket of the reverse transcriptase enzyme. Its molecular flexibility enables it to retain this binding capacity when mutations change the shape or electro-

static conditions of the binding site [23]. *In vitro* data demonstrated that TMC125 was highly effective against both wild-type virus and NNRTI-resistant strains [24]. However, the *in vitro* activity against wild-type virus was not dissimilar from the marketed NNRTI efavirenz, for which a viral load drop of 1.6 log<sub>10</sub> in 2 weeks has been reported [25]. Therefore, the *in vitro* activity of TMC125 alone does not entirely explain its excellent antiretroviral activity as observed *in vivo*.

One potential explanation could be that TMC125 has a more than fourfold higher exposure in the lymph nodes than in plasma, and possibly also in other reservoirs of HIV as has been demonstrated in dogs [26]. It is not clear whether the high level of tissue distribution is unique for TMC125 but it is conceivable that this may substantially contribute to its overall potency and its pronounced effect on the CD4 T-cell count.

Recently the importance of the early antiviral response as a predictor of long-term outcome of antiretroviral therapy has been discussed. Mittler *et al.* reported that the efficacy of antiretroviral therapy measured after 14 days of treatment correlates with the overall reduction in plasma HIV-1 RNA after 2 months [27].

Polis *et al.* demonstrated that a strong decline of plasma HIV-1 RNA in the first week of therapy is predictive of a long-term response and that a reduction in plasma HIV-1 RNA of less than about 0.6 log<sub>10</sub> after 6 days of therapy is associated with a poor outcome in all patients at week 12 [18]. We demonstrated earlier that this triple-class five-drug regime not only results in a faster decline of the plasma HIV-1 RNA [13] but also results in a stronger long-term suppression as compared to a standard triple regimen [28].

The apparent ability of TMC125 to substantially reduce the plasma HIV-1 RNA within only 7 days of monotherapy suggests that starting treatment with a TMC125-containing regimen could give a better suppression of HIV replication in the long-term. Future clinical trials with TMC125 in combination with other antiretrovirals are needed to support this initial, exciting finding.

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