Table 1. Plasma and CSF aciclovir concentrations in patients treated with iv aciclovir and/or oral valaciclovir

Patient	Duration into illness	iv aciclovir (8 hourly dose)	Oral valaciclovir (8 hourly dose)	Trough plasma (mg/L)	Peak plasma (mg/L)	Trough CSF (mg/L)	Peak CSF (mg/L)	CSF penetration (%)
1	7 weeks		250 mg (30 mg/kg)	0.6	4.9			
	4 months		250 mg (28 mg/kg)	0.8	4.1			
	8 months		250 mg (25 mg/kg)	0.5	2.5	0.3		60
2	2 weeks	500 mg/m^2		1.2		1		80
	4 weeks		250 mg (30 mg/kg)	0.3	3.5			
	6 weeks		375 mg (40 mg/kg)	0.7	10.2		0.9	9
	2 months		375 mg (38 mg/kg)	0.4	5.9			
	3 months		375 mg (38 mg/kg)	0.1[a]	5.7[a]		0.5[a]	9
3	3 weeks	500 mg/m^2		0.3	4.3	0.6		200
	5 weeks	500 mg/m^2		0.3	5.8	0.6		200
	2 months		260 mg (30 mg/kg)	0.7	7.2			
4	day 4	500 mg/m^2		0.7		0.6		85
5	day 14	500 mg/m^2		2.2	9.2	1.4		64

NB. The theoretical plasma trough target concentration was 0.44 mg/L.
[a]Missed dose prior to measurement.

of our knowledge is derived from data on three patients (two adults and one child).[8]

Oral valaciclovir was well tolerated in our very young children and can be considered for long-term treatment such as in relapsing HSV encephalitis or disease with focal destruction lesions on neuroimaging where prolonged iv aciclovir therapy is not practical and oral aciclovir has poorer bioavailability. Provided aciclovir concentrations are monitored and the administration of valaciclovir tolerated, the valaciclovir dose can be titrated upwards either to achieve plasma concentrations equivalent to those reported after a particular iv aciclovir administration dose or to a theoretically calculated target dose, as in our cohort.

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None to declare.

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Sustained HIV RNA suppression after switching from enfuvirtide to etravirine in the early access programme

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Sir,

The next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine (formerly known as TMC125) and the fusion inhibitor enfuvirtide have both shown improved efficacy over optimized background treatments in the DUET and TORO trials, respectively.[1–3] Due to the cost of enfuvirtide and the need for twice-daily injections, switching from enfuvirtide to etravirine could improve convenience and tolerability, and reduce treatment costs. Two recent pilot studies have shown sustained HIV RNA suppression, 7 months after switching from enfuvirtide to raltegravir in virologically suppressed patients.[4,5] A pilot study also showed sustained HIV RNA suppression for 6 months, after switching from enfuvirtide and protease inhibitors (PIs) to etravirine and darunavir/ritonavir, in 10 American patients.[6]

The TMC125-C214 trial (global etravirine early access programme) recruited triple class experienced patients who had received at least two previous PI-containing regimens. Patients with undetectable HIV RNA levels at the screening visit were permitted to switch from enfuvirtide to etravirine for either intolerance or simplification. The patients were allowed to optimize other parts of the background regimen at the time of switch from enfuvirtide to etravirine. Patients were followed up for HIV RNA, CD4 count and serious adverse events. All patients signed informed consent and the programme was approved by local and national ethics committees. We analysed 24 week data for 22 patients in Europe and 15 patients in Canada. Of these 37 patients, 11% were female and 95% were Caucasian, with a mean age of 48 years (range 36–62). The baseline mean CD4 cell count was 380 cells/mm^3 [95% confidence interval (CI): 312–449].

Thirty-six of the 37 patients (97%) used etravirine in combination with darunavir/ritonavir. Darunavir/ritonavir was used as a single boosted PI for 33 of the patients; two patients used a combination of darunavir/ritonavir with atazanavir and one patient used darunavir/ritonavir with tipranavir. Raltegravir was used for 62% of the patients, maraviroc in 16% and nucleoside analogues in 89%.

The patients were divided into two groups, shown in Table 1. Group 1 ($n=18$) included patients for whom the main change in antiretroviral treatment between screening and baseline was the switch from enfuvirtide to etravirine. The nucleoside analogues used remained the same between screening and baseline for these patients; six patients also switched from tipranavir/ritonavir to darunavir/ritonavir (owing to the pharmacokinetic interaction between tipranavir and etravirine). Group 2 ($n=19$) included patients with more extensive changes in their antiretroviral drugs, mainly for simplification and to improve tolerability: 17 out of the 19 patients (89%) also changed their PIs, 12 (63%) added raltegravir, 9 (47%) changed their nucleoside reverse transcriptase inhibitors and 3 (16%) added maraviroc.

All patients had HIV RNA levels of <50 copies/mL at baseline. Overall, the percentage of patients with HIV RNA suppressed to <50 copies/mL was 84% (31/37) at week 4, 86% (32/37) at week 12 and 95% (35/37) at week 24. Mean CD4 counts at week 24 were 406 cells/mm^3, a small rise from the baseline level. Table 1 shows HIV RNA levels for individual patients at week 24. All five patients with HIV RNA not <50 copies/mL at week 12 had HIV RNA levels just above the detection limit (50, 52, 52, 58 and 217 copies/mL). Of those with HIV RNA not <50 copies/mL at week 24, there was one patient with an HIV RNA level at 50 copies/mL and one patient with missing data at week 24—this patient had HIV RNA <50 copies/mL at the week 12 visit.

There were four serious adverse events reported in four different patients: myocardial infarction, chest pain, psychotic disorder and bacterial pneumonia. These were all judged to be unrelated to etravirine treatment by the investigators, and the dose of etravirine was not changed. There were no deaths during the 24 weeks of follow-up.

The results from the 18 patients in group 1 of this study suggest that etravirine may be an effective substitute for injectable enfuvirtide for reasons of either intolerance or patient preference. The vast majority of patients who switched from enfuvirtide to etravirine have sustained HIV RNA suppression at <50 copies/mL for up to 24 weeks of study, with stable or rising CD4 cell counts. The results from group 2 are more difficult to interpret: while the patients in this group maintained HIV RNA suppression, this could be partly explained by other drugs changed at baseline, as well as the replacement of enfuvirtide with etravirine. The use of etravirine in combination with darunavir/ritonavir, raltegravir or maraviroc is supported by pharmacokinetic drug–drug interaction trials[7,8] and pilot studies of 24 week efficacy.[9–11] In the future, using combinations of three of these newer drugs may lessen the need for using multiple nucleoside analogues, enfuvirtide and dual-boosted PIs.

For patients with prior virological failure on NNRTI-based antiretroviral therapy, it is important to check genotypic resistance tests before considering a switch to etravirine. For patients with full virological suppression on their current antiretrovirals, historical genotypic results would be needed to judge whether the patient's virus is fully susceptible to etravirine. A weighted genotypic algorithm is available to calculate the expected response rates by genotype during treatment with etravirine.[12] Genotypic resistance data may not always be available for these patients.

In summary, this pilot study suggests that a switch from enfuvirtide to etravirine in patients who are virologically suppressed and taking a wide range of other antiretrovirals led to sustained HIV RNA suppression for 24 weeks. Traditionally, enfuvirtide has been used in highly treatment-experienced patients and it is important to ensure that switches in treatment are done cautiously in this treatment group.

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Table 1. Antiretrovirals used at the screening visit (with enfuvirtide), during the trial (with etravirine) and HIV RNA data at week 24

Patient	Antiretrovirals used with enfuvirtide at screening	Antiretrovirals used with etravirine during the trial	HIV RNA week 24 (copies/mL)
Group 1 ($n=18$)			
1	TDF/FTC/EFV + DRV/r + RAL	TDF/FTC + DRV/r + RAL	<50
2	TDF/FTC + TPV/r	TDF/FTC + DRV/r	<50
3	TDF/FTC + TPV/r	TDF/FTC + DRV/r	<50
4	TDF/FTC + TPV/r	TDF/FTC + DRV/r	<50
5	DRV/r + RAL	DRV/r + RAL	<50
6	TDF/ZDV/3TC + TPV/r	TDF/ZDV/3TC + DRV/r	<50
7	TDF/3TC + ATV/r	TDF/3TC + DRV/r	<50
8	DRV/r + RAL	DRV/r + RAL	<50
9	TDF/FTC + DRV/r + RAL	TDF/FTC + DRV/r + RAL	<50
10	TDF/FTC + DRV/r + RAL	TDF/FTC + DRV/r + RAL	<50
11	TDF/FTC + DRV/r + RAL	TDF/3TC + DRV/r + RAL	<50
12	TDF/FTC + DRV/r	TDF/FTC + DRV/r	<50
13	ZDV/TDF/FTC + TPV/r + RAL	ZDV/TDF/3TC + DRV/r + RAL	<50
14	ddI/TDF/FTC + DRV/r	ddI/TDF/FTC + DRV/r	<50
15	TDF/FTC + DRV/r + RAL	TDF/FTC + DRV/r + RAL	<50
16	3TC + DRV/r + RAL	3TC + DRV/r + RAL	<50
17	ZDV/ABC/3TC + DRV/r	ZDV/ABC/3TC + DRV/r	<50
18	TDF/3TC + TPV/r	TDF/FTC + DRV/r	<50
Group 2 ($n=19$)			
1	TDF/FTC + TPV/r	TDF/FTC + DRV/r + RAL	<50
2	TDF + TPV/r	ABC/3TC + DRV/r + RAL	<50
3	TDF/3TC/ABC + FPV/r	TDF/3TC/ABC + DRV/r + RAL/MVC	<50
4	TDF/FTC + TPV/r	TDF/FTC + DRV/r + RAL/MVC	<50
5	3TC/ddI + TPV/r	ZDV/TDF/3TC + DRV/r	<50
6	TDF/FTC + TPV/r + RAL	DRV/r + RAL	<50
7	TDF/ABC/FTC/ZDV + TPV/APV/r	ZDV/ABC + DRV/r	<50
8	ABC + IDV/LPV/r	TDF/ABC/3TC + ATV/DRV/r	<50
9	ddI/TDF/3TC/ABC + LPV/FPV/r	TDF/3TC/ABC + DRV/r + RAL	<50
10	TDF/3TC + TPV/r	TDF/FTC + DRV/r + RAL	50
11	ABC/3TC + TPV/r	ABC/3TC + DRV/r + RAL	<50
12	ddI/3TC + ATV/SQV/r	3TC + RAL/MVC	[a]
13	ABC/3TC + DRV/r	ABC/3TC + DRV/r + RAL/MVC	<50
14	TPV/r + EFV	DRV/r + RAL	<50
15	d4T/3TC + LPV/r	ZDV/3TC + DRV/ATV/r	<50
16	TDF/ZDV/3TC + TPV/r	TDF/FTC + TPV/DRV/r	<50
17	TDF/FTC + SQV/FPV/r	TDF/FTC + DRV/r + RAL	<50
18	TDF/ABC/3TC + LPV/APV/r	TDF/ABC/3TC + DRV/r + RAL/MVC	<50
19	d4T/3TC + DRV/r + EFV	d4T/3TC + DRV/r + RAL	<50

TDF, tenofovir; FTC, emtricitabine; EFV, efavirenz; 3TC, lamivudine; ddI, didanosine; ABC, abacavir; IDV, indinavir; d4T, stavudine; ZDV, zidovudine; TPV/r, tipranavir/ritonavir; DRV/r, darunavir/ritonavir; LPV/r, lopinavir/ritonavir; FPV/r, fosamprenavir/ritonavir; ATV/r, atazanavir/ritonavir; SQV/r, saquinavir/ritonavir; APV/r, amprenavir/ritonavir; RAL, raltegravir; MVC, maraviroc.

[a]One patient had missing data at week 24 but had HIV RNA <50 copies/mL at the week 12 visit.

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Author contributions

M. L., E. R., E. F., S. De W. and A. C. participated in the recruitment of patients and reporting of data for these patients. All authors reviewed and approved the final version of the manuscript.

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Off-label use of antibiotics in hospitalized patients: focus on tigecycline

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Sir,

Tigecycline is the first of a new class of antibiotics named glycylcyclines and is active *in vitro* against a variety of Gram-positive and Gram-negative organisms, including vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, extended-spectrum β-lactamase-producing Enterobacteriaceae and multidrug-resistant (MDR) *Acinetobacter* spp.[1]

It has been approved by the US FDA for the treatment of complicated intra-abdominal infections (cIAIs), complicated skin and skin structure infections (cSSSIs)[1] and community-acquired bacterial pneumonia (CABP).[2]

Notwithstanding these indications, tigecycline's pharmacological and microbiological profiles encourage physicians' use of the drug for off-label indications.[3,4]

The definition of off-label use is not limited to prescribing an antibiotic for an indication that is not approved by regulatory authorities. The off-label use of a medication may include other parameters such as age, severity of illness, dose and route of administration and drug combinations, among others.[5]

Taking this into consideration, we have evaluated some characteristics of a group of patients treated with tigecycline for the approved indications (cSSSIs, cIAIs and CABP) and compared them with the patients included in the randomized clinical trials (RCTs) developed by the pharmaceutical company for each indication.

Between 16 September 2007 and 11 May 2009, I developed the LatinUser Project (Latin America Tigecycline Initial Use Registry), which included patients treated with tigecycline in 21 institutions from Argentina, Chile, Colombia and Ecuador. Patients were eligible for the LatinUser Project if they received tigecycline for $\geq$72 h and were not part of a clinical trial.

For the present analysis, patients who received tigecycline for approved indications (cSSSIs, cIAIs and CABP) were extracted from the LatinUser database. The following data were analysed for each patient: and compared with those from the RCTs for each indication (cSSSIs, cIAIs and CABP) (Wyeth Pharmaceuticals Inc., Philadelphia, PA, USA): (i) admission setting [general ward or intensive care unit (ICU)]; (ii) severity of illness at admission [measured by the APACHE II (Acute Physiology and Chronic Health Evaluation II) score]; (iii) source of infection; (iv) previous and concurrent antibiotic therapy (defined as a patient who received at least one dose of another