CONCISE COMMUNICATION

Dosing antiretroviral medication when crossing time zones: a review

Joseph M. Lewis[a,b], Alain Volny-Anne[c], Catriona Waitt[d], Marta Boffito[e] and Saye Khoo[d]

International tourism continues to increase worldwide, and people living with HIV and their clinicians are increasingly confronted with the problem of how to dose antiretroviral therapy during transmeridian air travel across time zones. No guidance on this topic currently exists. This review is a response to requests from patient groups for clear, practical and evidence-based guidance for travelling on antiretroviral therapy; we present currently available data on the pharmacokinetic forgiveness and toxicity of various antiretroviral regimens, and synthesize this data to provide guidelines on how to safely dose antiretrovirals when travelling across time zones.

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Introduction

Combination antiretroviral therapy (cART) can provide durable viral suppression of HIV infection and dramatically improve HIV-related mortality and morbidity [1]. High levels of adherence to therapy are necessary to achieve optimal viral suppression and patients are counselled against late dosing of their antiretrovirals in order to prevent treatment failure [2] and development of resistance [3]. Air travel across time zones can therefore present challenges in the optimum timing of medication administration, not only to minimize the chance of developing resistant virus, but also to minimize the risk of medication-related toxicity.

International tourism increased from 25 million international tourist arrivals worldwide in 1950 to 1.1 billion in 2013 [4]. Patients on cART are among these, benefitting from the improvement in survival and wellbeing offered by effective therapy [5]. However, no guidance on how to take medications when travelling across time zones exists, and there seems to be a lack of consistent advice from treating physicians, who, in our experience, are less likely to regard this as a problem than their patients. This review is a response to requests from patient groups for clear, practical and evidence-based guidance for travelling on cART.

It is essential to remember other vital considerations for HIV positive travellers, including pretravel vaccination and interaction of antiretrovirals with antimalarial chemoprophylaxis. Full consideration of these aspects of travel is beyond the scope of this review, but all HIV positive travellers are advised discuss any travel plans with

[a]Tropical and Infectious Diseases Unit, Royal Liverpool University Hospital, [b]Wellcome Trust Liverpool Glasgow Centre for Global Health Research, University of Liverpool, Liverpool, UK, [c]European AIDS Treatment Group, Brussels, Belgium, [d]Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, and [e]St Stephen's Centre, Chelsea & Westminster Foundation Trust, London, UK.

Correspondence to Joseph M. Lewis, BA, MA, MSc, MBBS, Tropical and Infectious Diseases Unit, Royal Liverpool University Hospital, Prescot St, Liverpool, L7 8XP, UK.

Tel: +0151 7063835; fax: +0151 706 5944; e-mail: joseph.lewis@liverpool.ac.uk
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their healthcare providers or a travel medicine specialist well in advance of travel. It may be beneficial to obtain contact details for local HIV support organizations at the travel destination, which may be able to offer advice in the event of unforeseen problems; online databases of such organizations are available (e.g. www.aidsmap.com/e-atlas).

Challenges of international travel with combination antiretroviral therapy – pharmacological and other considerations

Mammalian circadian rhythms are thought to be generated by 'pacemakers' within the hypothalamic suprachiasmic nuclei. Synchronization of the circadian rhythm to a 24-h day requires regular exposure of these pacemakers to environmental time clues, termed *zeitgebers* (time-givers), such as daylight, sleep and food. In the absence of *zeitgebers*, the human circadian rhythm graduates towards a 25-h cycle. Jet lag disorder occurs when rapid transmeridian travel causes circadian misalignment [6].

There are no data on the effect of transmeridian travel or jet lag disorder on drug metabolism. Diurnal variation in trough drug levels has been observed for some antiretrovirals, including lopinavir [7], atazanavir [8] and raltegravir [9] though no therapeutic relevance of this phenomenon has been demonstrated for any drug [10]. Thus, the major impact of long distance travel remains suboptimal dose spacing as a result of travelling (with opportunistic pill intake), and following arrival in a new time zone (where altered sleep patterns may impinge on the next due dose). Individuals vary in medication intake when travelling, ranging from missing multiple doses to rigid timekeeping which requires pill taking at awkward times.

Is it possible therefore to make recommendations for medicine intake during travel which are pragmatic, safe and evidence based? Pharmacokinetic data provide the best guidance for forming recommendations through understanding of the relationship between drug concentration and therapeutic effect or toxicity, and estimation of tolerance for late or early dosing around air travel. The over-arching need is for pragmatic management, bearing in mind the intended purpose of travel is to be productive or pleasurable; any recommendations should not therefore act as a barrier to travel, especially as there are no proven cases travel-induced erratic antiretroviral dosing resulting in development of resistance and treatment failure.

Clinical studies which have observed a pharmacokinetic–pharmacodynamic relationship (e.g. efavirenz [11], nevirapine [12], lopinavir [13], raltegravir [14]) have defined antiretroviral minimum effective concentrations (MEC). For other drugs, an in-vitro inhibitory concentration ($IC_{50/90/95}$) adjusted for protein binding (e.g. darunavir [15], rilpivirine [16]) informs the dosing schedule. Nucleoside reverse transcriptase inhibitors (NRTIs) require intracellular activation to active triphosphate anabolites, the levels of which correlate poorly with parent drug plasma levels; target levels of NRTIs are therefore poorly defined [17]. The *pharmacokinetic forgiveness* [18] is the time between the next due dose (at which time the drug concentrations are at Cmin) and the point at which the concentration of drug falls below the estimated MEC. Knowledge of the forgiveness of a drug therefore allows a clinician to advise a patient on how long a dose may safely be delayed during travel.

Delayed dosing beyond the pharmacokinetic forgiveness of a drug and subsequent subtherapeutic drug levels can predispose to viral resistance and treatment failure. However, early dosing may cause supratherapeutic drug levels and toxicity. In addition, many antiretrovirals (e.g. rilpivirine, efavirenz, tenofovir, elvitegravir and boosted protease inhibitors) are ingested with specific recommendations for food intake, which may be problematic on commercial flights when meal times are fixed.

Characterizing the forgiveness of an antiretroviral drug regimen: what data are available?

The best data for estimating forgiveness of an antiretrovirals regimen derive from 'tail' studies tracking drug elimination following treatment cessation in healthy volunteers where median time to reaching MEC can be calculated [19–23]. Where tail studies have not been undertaken (e.g. nevirapine, etravirine, raltegravir, maraviroc), an estimate of regimen forgiveness can be extrapolated using average drug half-lives from standard pharmacokinetic studies, though this is likely to be less accurate. Indirect estimates of forgiveness can also be derived from adherence and treatment interruption studies. Here we consider the available data from each of these sources in turn.

Tail data in healthy volunteers is available for boosted atazanavir [19,20], boosted lopinavir once and twice daily [20], boosted darunavir [19], co-formulated efavirenz/tenofovir/emtricitabine [21], dolutegravir [22], co-formulated elvitegravir/cobicistat/tenofovir/emtricitabine [22] and co-formulated rilpivirine/tenofovir/emtricitabine [23] and is presented in Table 1. Although MECs for NRTIs are not established, the pharmacokinetic parameters of the active intracellular metabolites of tenofovir and emtricitabine have been established in one tail study, where both were found to have long terminal half-lives of 164 and 39 h, respectively [21]. This gives some reassurance that regimens containing these long-acting NRTIs provide a further element of forgiveness for late dosing.

Tail data are not available for maraviroc, raltegravir, nevirapine or etravirine. An estimation of pharmacokinetic forgiveness can be made for these drugs from data on

Table 1. Data from tail studies showing proportion of trial participants with plasma drug concentrations below estimated MEC at time in hours post drug cessation.

Drug	ATV/r OD	ATV/r OD	LPV/r BD	LPV/r OD	DRV/r OD	EFV OD	EVG/COBI OD	DTG OD	RPV OD
Dose	300 mg/100 mg	300 mg/100 mg	400 mg/100 mg	800 mg/200 mg	800 mg/100 mg	600 mg	150 mg/150 mg	50 mg	25 mg
MEC	150 ng/ml	150 ng/ml	1000 ng/ml	1000 ng/ml	550 ng/ml	1000 ng/ml	45 ng/ml	64 ng/ml	50 ng/ml[a]
Reference	Boffito 2008 [20]	Boffito 2011 [19]	Boffito 2008 [20]	Boffito 2008 [20]	Boffito 2011 [19]	Jackson 2013 [21]	Elliot 2015 [22]	Elliot 2015 [22]	Dickinson 2015 [23]
Participants, *n/N* with plasma drug concentration below MEC post drug cessation									
Time (hours)									
12	0/16		0/16	0/16					
16	0/16		2/16	0/16					
20	0/16		10/16	0/16					
24	0/16		13/16	7/16			0/17	0/17	2/18
30	2/16	0/17	15/16	15/16	3/17				
36	5 /16	8/17	16/16	16/16	8/17		11/17		6/18
48	11/16	12/17	16/16	16/16	15/17	5/16	16/17	0/17	7/18
60	16 /16	15/17	16/16	16/16	16/16			1/17	
72	16 /16		16/16	16/16				1/17	11/18
84						8/16			

ATV/r, atazanavir/ritonavir; BD, twice daily; DRV/r, darunavir/r; DTG, once-daily dolutegravir; EFV, efavirenz; EVG/COBI, elvitegravir/cobicistat; LPV/r, lopinavir/ritonavir; MEC, minimum effective concentration; OD, once-daily; RPV, rilpivirine.
[a]MEC for rilpivirine is not well defined but 50 ng/ml has been suggested; interpret results with caution.

mean trough concentrations, half lives and estimated MECs [12,24–29].

Data from treatment interruption studies can also provide an estimate of the forgiveness of a cART regimen. The five-days-on two-days-off (FOTO) study assessed the efficacy (in terms of virological suppression) of a FOTO strategy for 30 HIV positive individuals on cART. At 48 weeks 10/10 patients on efavirenz regimens were virally suppressed, as were 8/9 patients of nevirapine-based regimens, and 7/9 patients on protease inhibitor-based (largely lopinavir-based) regimens [30]. This provides some reassurance as to the forgiveness of these cART agents.

Toxicity and genetic barrier to resistance

Significant toxic effects are unlikely for the majority of antiretrovirals if a dose is taken a few hours early in the context of international travel. Significant symptoms from overdose of nevirapine have only been reported at 800 mg or above [27]. Mild symptoms only were noted in a massive lopinavir overdose of 270 Kaletra tablets [31]. Single doses of darunavir up to 3200 mg and atazanavir up to 1200 mg have been administered to healthy volunteers with no apparent ill effects [32,33]. Data on overdose of etravirine, rilpivirine, raltegravir and elvitegravir are not available but clinically important toxicity of these antiretrovirals is uncommon [34].

Early dosing of efavirenz and maraviroc may be problematic; increased efavirenz dose may enhance neuropsychiatric toxicity [35], which is especially undesirable at check-in. Maraviroc has been administered up to 1200 mg in clinical studies, and the dose limiting effect is postural hypotension [24], which could also be problematic whilst travelling.

The final important consideration in advising patients how to alter the administration of cART when crossing time zones is the genetic barrier to resistance of their medications. A low genetic barrier to resistance means resistant virus may generate more rapidly when the level of drug is below the MEC; efavirenz, nevirapine, rilpivirine and raltegravir fall into this category; maraviroc, etravirine and elvitegravir have a slightly higher barrier to resistance, but still significantly lower than the protease inhibitors and dolutegravir [36]. Any functional antiretroviral monotherapy causes increased risk of generating viral resistance; this is of potential concern with late dosing of protease inhibitors when they are used as monotherapy, but also in the late dosing of cART when individual components of a regimen have different half-lives.

Advice for travellers

There are two potential issues to tackle with regard to time of dosing; firstly, how and when to dose during a long distance flight across time zones; and secondly, how

Table 2. Recommendations for antiretroviral intake for transmeridian travel more than 8 h.

	Drug	Dosing recommendation for travel
Likely to be tolerant of late dosing	Tenofovir, emtricitabine, lamivudine, abacavir, didanosine	OD dosing – adjust intake to dose before travel, and after arrival. For efavirenz, dosing immediately prior to departure should be avoided – instead dosing can be safely stretched from previous evening (from FOTO data)
	Efavirenz OD	BD dosing – adjust intake to dose before departure (for flights of 12 h or less), or take an extra dose in-flight at a convenient time for longer duration flights. Take next dose after arrival
	Nevirapine OD or BD	All subsequent dosing according to new time zone
	Rilpivirine OD	
	Boosted atazanavir[a] OD	
	Boosted darunavir[a] OD or BD	
	Boosted elvitegravir[a] OD	
	Dolutegravir OD or BD	
	Maraviroc OD[a] or BD	
Likely to be moderately tolerant of late dosing	Stavudine, zidovudine lopinavir/ritonavir BID	As above for BD dosing. All subsequent dosing according to new time zone
	Raltegravir BD	
	Darunavir/ritonavir monotherapy	
Likely to be poorly tolerant of late dosing	Lopinavir/ritonavir OD	Take an extra dose in-flight. All subsequent dosing according to new time zone
	Unboosted atazanavir	
	Monotherapy with boosted atazanavir or lopinavir	

BD, twice daily; FOTO, five-days-on, two-days-off; OD, once-daily.
[a]Boosted with ritonavir or cobicistat.

to shift the medication regimen to a new time zone. The longest recorded commercial flight is just under 19 h from Newark to Singapore [37]. Using this longest possible flight time, we suggest general principles to guide patients taking cART when crossing time zones.

1. The risk of travel is lowest when the patient is stable on their cART with a well suppressed viral load; for individuals whose viral load is unsuppressed a careful risk assessment on a case-by-case basis should be carried out, and the following recommendations may not be appropriate.
2. Many travellers have already established a system for taking their medication whilst travelling; if this is successful without evidence of virological rebound, it can be safely continued.
3. Due to confusion regarding times and fixed mealtimes, we recommend avoidance of in-flight dosing if possible and safe to do so.
4. Although in-flight dosing can be avoided for many regimens, the MECs for patients with known resistant virus are likely to be higher and consideration should be given to dosing in-flight.
5. In addition, complex itineraries with multiple time zone shifts in the space of a few days may require more careful planning and may require in-flight dosing.
6. Get into the new time zone as quickly as possible; dosing according to country of origin is likely to result in confusion and poor adherence. Compensate with an extra dose on arrival if necessary.

Using these general principles and data on the forgiveness of different antiretrovirals, we suggest specific dosing recommendations by antiretroviral for transmeridian travel more than 8 h (Table 2).

Conclusion

Pharmacokinetic data to guide clinicians and their patients in dosing antiretrovirals when crossing time zones are incomplete; nevertheless, this review summarizes and interprets existing data, offering a framework for safe administration. Clinicians should not neglect the other aspects of a pretravel consultation for the HIV positive traveller, who should be encouraged to ensure they have an adequate supply of tablets, consider pretravel vaccinations and malarial chemoprophylaxis when necessary, along with a standard assessment of the risks of travel to any destination. The pharmacokinetic profile and side-effect profile of the majority of the reviewed antiretrovirals, in conjunction with the fact that there are no proven case reports of travel-induced erratic dosing of antiretrovirals bringing about treatment failure should reassure people living with HIV and their physicians that transmeridian travel across time zones can be safe, and enjoyable.

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Conflicts of interest

There are no conflicts of interest.

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