TDM of antiretrovirals in 2017

Why?

Stefano Bonora

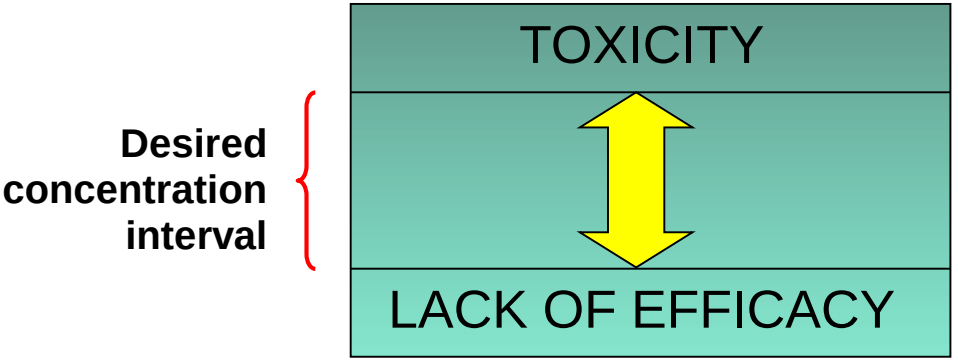
University of Torino

The key concept of Therapeutic Drug Monitoring (TDM) is to individualised drug dosage to attain certain target plasma concentrations

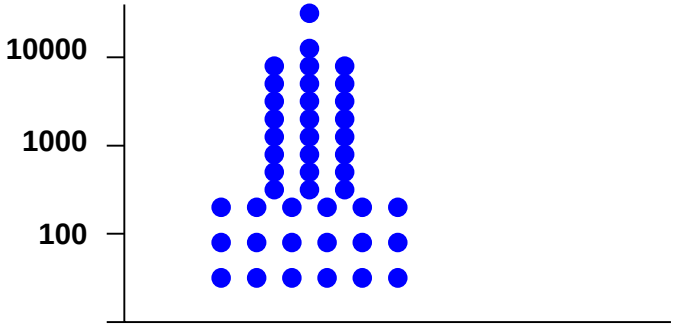
TDM in Antiretroviral Therapy

The rationale for TDM of antiretrovirals points on two main characteristics:

a) Relationships between drug concentration and immunovirological benefit - and in some cases, toxicity - have been established;



b) Available clinical data show significant interpatient variability at equal dose intake



DHHS 2016

Use of TDM to monitor ARV concentrations in a patient requires the following:

• quantification of the concentration of the drug, usually in plasma or serum;

• determination of the patient's pharmacokinetic characteristics;

• integration of information on patient adherence;

• interpretation of the drug concentrations; and

• adjustment of the drug dose to achieve concentrations within the therapeutic range, if necessary

Italian Guidelines 2016

TDM PROs

- data showing that considerable interpatient variability in drug concentrations exists among patients who take the same dose;
- data indicating that relationships exist between the concentration of drug in the body and anti-HIV effect and, in some cases, toxicities;
- data from small prospective studies demonstrating that TDM improved virologic response and/or decreased the incidence of concentration-related drug toxicities

ITALIAN GUIDELINES 2016

DRUGS	EFFICACY	TOXICITY	RECCOMENDATION (POWER/EVIDENCE)	RIFS
Darunavir§ (600 mg BID)	3300 (1255-7368)	-	[BII]	[14]
Fosamprenavir	400	-	[BII]	[6]
Atazanavir	150	850	[BII]	[12]
Indinavir	100	500	[AI]	[9,10]
Lopinavir	1000	-	[BII]	[6]
Saquinavir	100-250	-	[BII]	[56
Efavirenz	1000	4000	[AII]	[7,11]
Etravirina§	275 (81-2980)		[CIII]	[8]
Nevirapina	1000	-	[BII]	[44]
Tipranavir*	20.500	-	[BII]	[13]
Raltegravir§	72 (29-118)		[CIII]	[15]
Maraviroc*	>50	-	[BI]	[17]

Italian guidelines 2016

TDM CONs

- lack of large prospective studies demonstrating that TDM improves clinical and virologic outcomes
- lack of established therapeutic range of concentrations for all ARV drugs
- intrapatient variability in ARV drug concentrations;
- lack of widespread availability of clinical laboratories
- shortage of experts to assist with interpretation of ARV concentration data..
- STR and coformulations do not allow dose adjustment

Scenarios for use of TDM

(DHHS 2016, Italian Guidelines 2016)

- Clinically significant drug-drug or drug-food interactions

- Changes in pathoshysiological states that may impair GI, hepatic, or renal function, thereby altering PK

- Persons such as pregnant women who may be at risk for virological failure as a result of their PK characteristics

- In treatment experienced persons

- Use of alternative dosing regimens

- Concentration-dependent toxicities

- Lack of expected virological response

6.2.2.2 Rationale

Therapeutic drug monitoring (TDM) has been shown to be valuable in optimising the management of certain individuals; however, the general utility of this test in those receiving ART has been poorly assessed. With the marked improvement in efficacy and tolerability of modern ARV regimens, the role of TDM in clinical management has also evolved. A Cochrane review of randomised controlled trials [1] suggested little value when used unselectively. However, TDM may aid the management of vulnerable populations or complex clinical situations.

- *Monitoring adherence*. While detection of drug at therapeutic or even high plasma concentrations does not exclude low adherence, absence of measurable drug, or else very low levels of drug, strongly suggest lack of medication intake, particularly in the absence of evidence of significant malabsorption. Here, TDM should rarely be interpreted in isolation, but rather integrated with virological rebound, particularly in the absence of any resistance mutations and other features in the history that suggest risk for low treatment adherence.
- *Optimising treatment in vulnerable PLWH*. In vulnerable PLWH (e.g. children, pregnant women [2] and individuals with extremes of body mass index) or in specific clinical situations (e.g. liver and renal impairment, treatment failure, drug interactions both foreseen and unanticipated, malabsorption, suspected non-adherence and unlicensed once-daily dosing regimens). In these scenarios, the aim is to optimise dosing based either on known efficacy or toxicity cut-offs, or else to achieve the range of plasma concentrations encountered in individuals without these factors, who have been recruited to pharmacokinetic studies at licensed treatment doses that are known to be both safe and efficacious.
- *Managing drug interactions (see above)*. Where the HIV drug has the potential to be adversely affected by another drug, and the combination is unavoidable, TDM may be used either to manage that interaction, or else discount a significant interaction in a particular individual.
- *Other situations*. Knowledge of plasma drug concentrations may be clinically useful when evaluating whether there is scope for treatment simplification, or else confirming or refuting impaired drug absorption as a reason for virological failure.

17:00 Clinical notes: TDM of antiretrovirals in 2017 **(Chair G. Di Perri)**

- why? **(S. Bonora)**
- when? **(C. Alcantarini, C. Montrucchio)**
- how? **(A. D'Avolio)**