

Durability of viral suppression according to self-reported non-adherence and antiretroviral plasma levels

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Abstract

Background. Both self-reported non-adherence (ADH) and sub-optimal plasma drug concentration (PDC) has been independently associated with virological failure, however it is not yet defined a threshold in these two determinants for an increasing risk of rebound in patients with virological success.

Methods. Longitudinal cohort analysis. Self-reported ADH rate was calculated as the number of pills taken divided by the number prescribed over the last 3 days. Plasma levels of NRTI, PI and NNRTI were concurrently assessed. A pharmacokinetic score (PKS) from 0 to 3 was derived for NNRTIs/Pis, identifying undetectability (0) and sub-optimal (1), optimal/expected (2), and higher than optimal/expected (3) ranges of concentration. NRTI backbone was scored 0 or 1 according to detectability of drugs adjusted for half-life. An overall marker of PDC was calculated as the number of classes with PKS >1 in current regimen.

Results. 142 patients (pts) with a viral load ≤80 copies/mL at baseline (time of plasma concentration test) were included in this analysis. Crude rates (per 100 pys) of virological rebound (VR) were 11.0 (95% CI: 6.3-17.9) in pts with 100% self-reported ADH, 24.1 (95% CI: 9.7-49.7) in those with 90-99% ADH, and 8.3 (95% CI: 0.2-4.6) in those with <90% ADH. According to PDC, pts without any class with PKS ≥1 had the greatest incidence of VR (75.0; 95% CI 34.3-142.4) compared with those with 1 (11.5; 95%CI 4.2-25.1) or 2 (8.0 ; 95%CI 3.7-15.3) classes with PKS ≥1. In a multivariable Poisson model, the only factors associated with VR were reporting 90-99% ADH (8.14 compared to 100% ADH; 95%CI 2.18-30.30, p=0.002) and classes of antiretrovirals with detectable concentrations (0.27 per each class with PKS ≥1; 95%CI 0.11-0.63, p=0.003). None of the scores for individual drug classes were significantly associated with the outcome if considered alone. There was a trend for the association between ADH and VR to be stronger in pts receiving single-PI (RR=8.14 95%CI: 2.18-30.30) than in those receiving NNRTI (RR=2.98, 95% CI: 0.36-24.8, p-value for interaction=0.17).

Conclusions. Pts reporting 90% to 99% ADH, even if with undetectable viremia at questionnaire, were at remarkably increased risk of subsequent failure compared to pts declaring perfect ADH. A global score of PDC that incorporates all antiretroviral classes, including a half-life adjusted score for NRTI, seems to be more predictive than concentration from any singular drug class.

Background

- Achieving and maintaining maximal and durable suppression of viral load are primary goals of antiretroviral therapy.
- Virological rebound has been attributed to several factors: poor adherence, inadequate concentration of antiretrovirals, selection of drug-resistant variants and low antiviral potency, and possibly specific drugs
- Both self-reported non adherence and sub-optimal plasma drug concentration have been independently associated with virological rebound, but up to now it is not yet defined a threshold in these two determinants for an increasing risk of viral rebound in patients with initial virological success
- The association between low plasma drug levels and inferior virological response has been demonstrated for both PIs and NNRTIs, whereas the association between low adherence and virological outcome has been clearly established only for therapies containing PI.
- The prognostic role of both plasma drug levels and self-reported adherence to predict virological rebound according to drug class exposure has not been evaluated.

Objectives

- To define a threshold in both self-reported adherence and drug plasma levels as determinants for an increasing risk of viral rebound in patients with virological success
- To evaluate the prognostic role of these two variables to predict virological rebound according to drug class exposure

Methods

- AdiCoNA Study is a nested study within the I.Co.N.A. (Italian cohort naïve from antiretrovirals) cohort addressing adherence to antiretroviral therapy
- Inclusion criteria:
 - Receiving HAART for at least 1 month
- Exclusion criteria:
 - Hospitalisation at enrolment
 - ADC >3
- Adherence assessment :
 - Self-reported, previously validated, questionnaire
 - Self-reported questionnaire was repeated at baseline, after 3 months and subsequently every 6 months
 - Non-adherence: percentage of pills taken divided by the number of those prescribed over the last 3 days

Methods

- Pharmacokinetics analysis :
 - At the time of each adherence questionnaire, a blood sample was taken to evaluate plasma concentrations of antiretrovirals.
 - Plasma drug levels of all antiretrovirals were determined by a validate SPE-HPLC system.
 - For each class of antiretroviral used at baseline, a pharmacokinetic score (PKS) was established.
 - NNRTIs/Pis PKS (see Table) was defined as:
 - 0 = undetectable levels: below limit of detection.
 - 1 = sub-optimal levels: detectable but below Minimum Effective Concentrations, MECs)
 - 2 = optimal/expected levels : between MEC and grade 3.
 - 3 = higher than optimal/expected levels: above upper limit of therapeutic range, if available (IDV and EFV), or above a recognised cut off of toxicity (NVP) or above the median concentration reported in literature (NFV, SQV, LPV/r)

Grading of PKS for NNRTIs and PIs

	EFV	NVP	SQV	IDV	LPV	NFV
0	ND	ND	ND	ND	ND	ND
1	50*-1000	5*-3400	15*-150	15*-100	50*-1000	30*-800
2	1000-4000	3400-6000	150-500	100-500	1000-5500	800-2000
3	>4000	>6000	>500	>500	>5500	>2000

All the values are expressed in ng/ml; *limits of quantification; C_{ough} samples are considered except for efavirenz (range 8-20 hrs after intake)

- NRTIs PKS (see Table) was calculated as a qualitative score.
- Considering that i) 3TC and TDF have a more prolonged half life as compared to other NRTIs, thus allowing their reliable measurement at the end of the dosing interval, ii) 3TC and/or TDF were taken by more than 80% of pts, we adopted the detection of these drugs (limits of detection 10 ng/ml) as a marker of intake of the whole NRTI backbone/regimen.
- In case of a 3TC/TDF-free backbone, the detection of at least one NRTIs (d4T, ddI, AZT, ddC) was considered as a marker of recent intake, while in case of undetectability no conclusions could be drawn, because of the short plasma half-life of these drugs.

Grading of PKS for NRTI

	3TC and/or TDF-containing backbone	3TC and TDF-free backbone
0	3TC and/or TDF undetectable*	NA
1	3TC and/or TDF detectable*	any NRTI detectable*

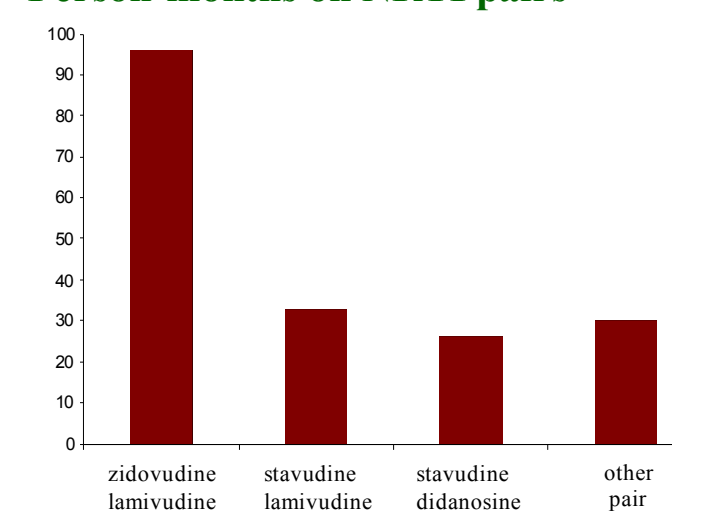
*limits of detection of any NRTI/NRTI: 10 ng/ml; NA : in case of 3TC or TDF-non containing regimen and no NRTIs detectable, grading was not applicable

- Data analysis :
 - All patients with undetectable viral load (≤80 cps/ml) at the time of a questionnaire (baseline) were included in this analysis
 - Crude risk of virological rebound (the date of rebound was defined as the time of first VL>400 cps/mL after baseline) was calculated according to self-reported adherence and plasma drug concentration
 - Multiple Poisson model included the following variables: self-reported adherence, NRTI-PKS, NNRTI- or PI-PKS, whether naïve when started HAART, total exposure to antiretroviral therapy, current use of specific NRTI pair and specific third drug (among efavirenz, abacavir, lopinavir, nelfinavir, indinavir and nevirapine)
 - A sensitivity analysis in the subgroup of subjects with confirmed virological failure (two consecutive VL>400 cps/mL) was also performed

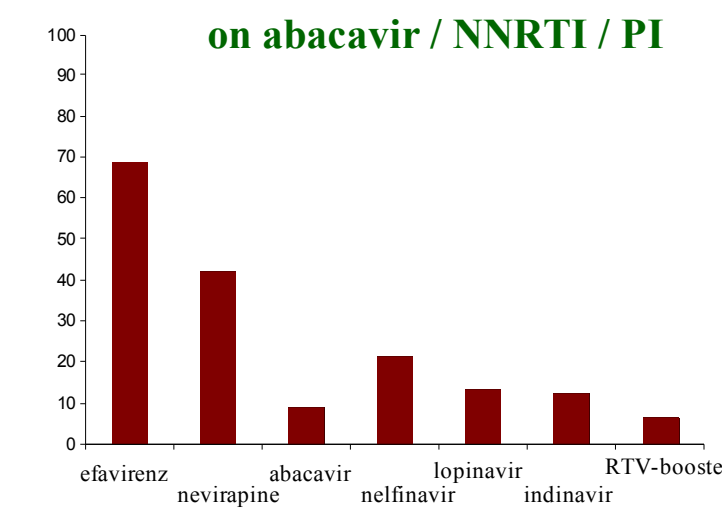
Results

General characteristics	N=142
Gender, Females (<i>n</i> , %)	46 (32.4%)
Age (years), <i>median (range)</i>	37 (23-62)
HIV transmission group (<i>n</i> , %)	
- MSM	34 (23.9%)
- IDU	43 (30.3%)
- Heterosexual	57 (40.1%)
Viral load at HAART, log ₁₀ cps/mL <i>median (IQR)</i>	4.71 (3.98-5.35)
CD4 count at HAART, cells/μl <i>median (IQR)</i>	288 (100-450)
Months since HAART at baseline, <i>median (IQR)</i>	36 (20-53)
Date of questionnaire, <i>median (IQR)</i>	Sep 02 (Feb 02 – Jan 03)
Months of follow-up, <i>median (IQR)</i>	13 (9 – 22)
Antiretroviral therapy at baseline (<i>n</i> , %)	
NRTIs: - zidovudine	80 (56.3%)
- lamivudine	113 (79.6%)
- didanosine	23 (16.2%)
- stavudine	53 (37.3%)
- abacavir	11 (7.8%)
- zalcitabine	2 (1.4%)
- tenofovir	6 (4.2%)
Pis: - lopinavir/r	14 (9.9%)
- nelfinavir	17 (12.0%)
- other RTV-boosted	7 (4.9%)
- indinavir	17 (12.0%)
NNRTIs: - efavirenz	45 (31.7%)
- nevirapine	34 (23.9%)

Person-months on NRTI pairs



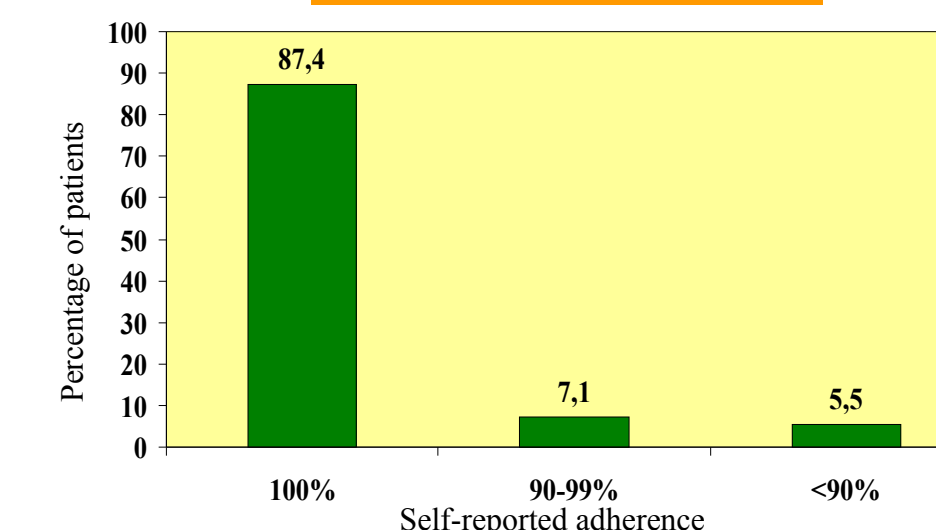
Person-months on abacavir / NNRTI / PI



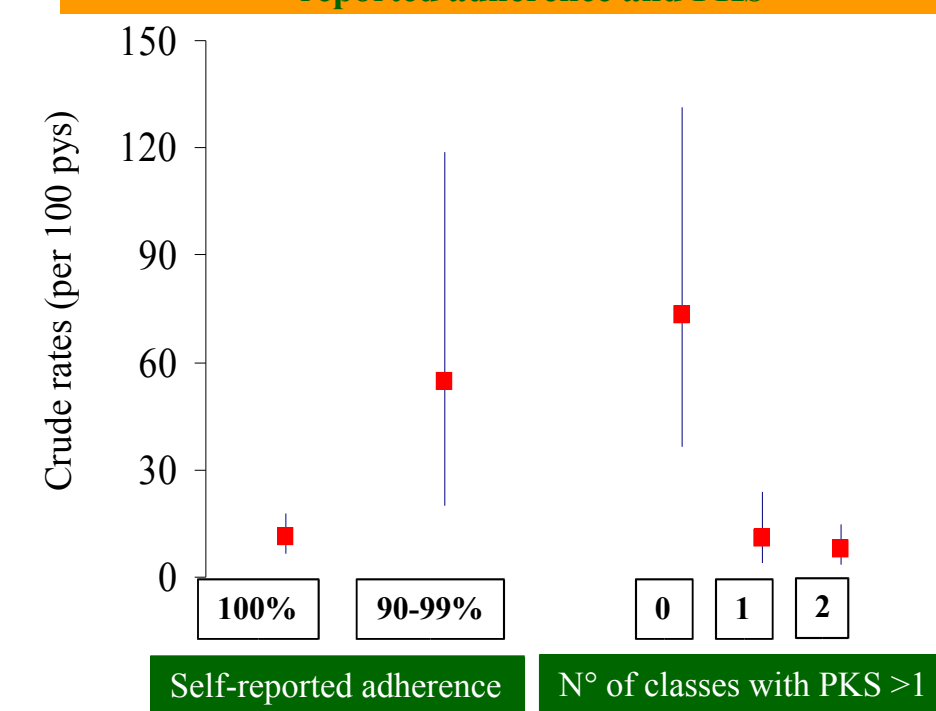
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Self-reported Adherence



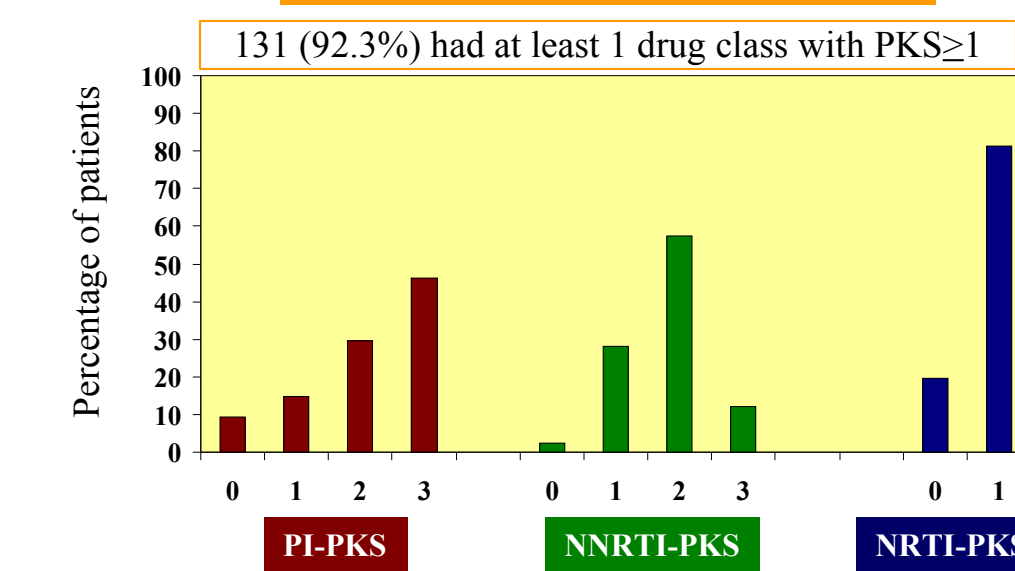
Crude rates of virological rebound according to self-reported adherence and PKS



Predictors of virological rebound according to self-reported adherence and PKS by antiretroviral classes

	RR (95% CI)	P
Self-reported adherence		
- 90-99% vs 100%	7.14 (1.92-26.6)	0.49
in pts receiving PI at bl		
- 90-99% vs 100%	2.75 (0.33-22.9)	(interaction)
in pts receiving NNRTI at bl		
PI-PKS ≥1 vs. 0	0.36 (0.06-2.28)	0.28
NNRTI-PKS ≥1 vs. 0	0.34 (0.06-2.04)	0.24
NRTI-PKS ≥1 vs. 0	0.33 (0.11-0.97)	0.04

Pharmacokinetics Characteristics



Predictors of virological rebound at multivariable Poisson model (1)

	RR (95% CI)	P
Self-reported adherence		
- 100%	1	
- 90-99%	8.09 (2.29-28.50)	0.001
N° of drug classes with PKS ≥1 (per additional class)	0.34 (0.16-0.72)	0.003

- No significant association with any of the other variables included in the model (i.e. naïve when started HAART, total exposure to antiretroviral therapy, current use of specific NRTI pair and specific third drug) was found.
- Results from the sensitivity analysis in the subgroup of subjects with confirmed virological failure (two consecutive VL>400 cps/mL) were similar to those reported above (data not shown)

Results

- Our study confirm that both self-reported non-adherence and sub-optimal plasma drug concentration were independently associated with a higher risk of virological rebound
- Patients reporting 90% to 99% adherence, even if with undetectable viremia at questionnaire, were at higher risk (8 fold increase) of subsequent failure compared with those declaring perfect adherence.
- Our data seem to suggest that this risk may be higher in patients who had achieved suppression on a PI-containing as compared to NNRTI-containing regimens but more evidence is needed
- A global score of plasma drug concentrations that incorporates all antiretroviral classes, including a half-life adjusted score for NRTI, seems to be more predictive of viral failure than concentration from any singular drug class.
- Even in patients who had initially achieved virological success, a great effort should be made to constantly monitor and improve adherence.