Longer term follow up of protease inhibitor-based dual antiretroviral therapy (PIDAT) in clinical practice

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Background

- Protease inhibitor-based dual antiretroviral therapy (PIDAT) is being evaluated in a number of clinical studies as both a naïve and switch/maintenance strategy in HIV-1 infected patients.
- Long term maintenance with PIDAT regimens, in particular nucleoside sparing regimens, may offer some toxicity benefits, and potential cost savings.
- We looked at longer term outcome of this paradigm as a switch/maintenance strategy within our large HIV cohort.

Methods

- Patients switching to a single protease inhibitor (PI/r) plus one other ARV (excluding PI/r) from 2004 to 2011 were identified from our HIV database.
- Treatment history and indication for switch were identified.
- Virological outcomes were assessed for those with the potential for 96 weeks or more follow up using snapshot analysis (+/-10 weeks).
- Single switch of PI/r or other drug was allowed if maintained PIDAT. Patients prescribed PIDAT as their first ART regimen were excluded from this analysis.
- Outcomes at 144 weeks were analysed for those with sufficient follow up.

Results (1)

Table 1: Characteristics of patients switching to PIDAT

	Specific PIDAT regimens				
	Total	NRTI	NNRTI	INI	CCR5-A
Prescribed PIDAT (N [%])	133	23 (17)	75 (56)	5 (4)	30 (23)
Demographics					
Age	45 [27, 69]	41 [31, 69]	46 [27, 65]	45 [36, 66]	45 [33, 63]
Male	94 (71)	16 (70)	50 (67)	3 (60)	25 (83)
Ethnicity					
White	86 (65)	14 (61)	46 (61)	4 (80)	22 (73)
Black	31 (23)	3 (13)	21 (28)	1 (20)	6 (20)
Other	16 (12)	6 (26)	8 (11)	0 (0)	2 (7)
Risk					
MSM	82 (61)	15 (68)	45 (58)	1 (33.3)	21 (69)
Heterosexual	46 (33)	7 (22.7)	28 (36.8)	3 (50)	8 (27.6)
Blood products	2 (2.3)	0 (4.5)	1 (1.3)	0 (0)	1 (3.4)
IVDU	3 (2.3)	1 (4.5)	1 (1.3)	1 (16.7)	0 (0)
HIV history					
Number years on ART	11.7 [0.1, 22.6]	8.7 [0.9, 19.5]	12.7 [0.9, 21]	10.0 [6.5, 14.0]	10.9 [1.5, 22.6]
Nadir CD4	135 [1, 642]	146 [7, 403]	135 [3, 642]	50 [20, 171]	160 [1, 598]
N prior ART regimens	7 [1, 24]	7.5 [1, 17]	8 [1, 19]	7 [1, 24]	6 [1, 16]
At switch					
VL<50c/mL	103 (79)	20 (87)	59 (79)	5 (100)	19 (63)
Time VL<50c/mL prior, years	4.1 [0, 12.6]	2.4 [0, 7.8]	5.2 [0, 12.6]	0.4 [0.01, 5.7]	2.4 [0, 9.49]
CD4 (cells/µl)	618 [107, 2320]	537 [107, 2320]	642 [109, 1601]	344 [211, 1066]	632 [189, 1393]
% CD4<200 (cells/µl)	5 (4)	2 (9)	1 (1)	0 (0)	2 (7)
Resistance prior to switch					
Nil	52 (39)	14 (64)	24 (35)	2 (40)	11 (38)
NRTI	44	5	25	2	12
NNRTI	24	4	8	0	12
PI	13	2	8	0	3

Numbers expressed as number (%) or median [range]

Table 2: Prior ARV combination before switching to PIDAT

Prior Combination	Number switching to specific PIDAT regimens, N (%)				
	Total	NRTI	NNRTI	INI	CCR5-A
Dual PI/r	**52 (39)**	**7 (30.4)**	**39 (52.0)**	**2 (40.0)**	**4 (13.3)**
Dual PI/r only	1	0	1	0	0
+NRTI	25	7	13	1	4
+NNRTI	23	0	23	0	0
+INI	1	0	0	1	0
+other	2	0	2	0	0
PI/r+2NRTI	**33 (24.8)**	**13 (56.5)**	**8 (10.7)**	**1 (20)**	**11 (37)**
NNRTI+2NRTI	**7 (5.2)**	**0 (0)**	**5 (6.7)**	**0 (0)**	**2 (6.7)**
PI/r monotherapy	**16 (12)**	**2 (8.7)**	**3 (4.0)**	**0 (0)**	**11 (37)**
LPV/r	3	1	0	0	0
DRV/r	13	1	3	0	10
Other	**25 (18.7)**	**1 (4.3)**	**20 (26.7)**	**2 (40.0)**	**2 (6.7)**
PI/r+NNRTI+NRTI	19	1	17	1	0
Other	5	0	2	1	2
uPI+2NRTI	1	0	1	0	0

Results (2)

Table 3: Primary indication for switch to PIDAT

	Number switching to PIDAT,				
Indication	Total (n [%])	NRTI	NNRTI	INI	CCR5-A
Rationalisation of dual PI/r	37 (27.8)	4 (17.4)	31 (41.3)	1 (20.0)	1 (3.3)
Pill burden	27	4	23	0	0
GI side effects	6	0	5	1	0
Hyperlipidaemia	4	0	3	0	1
Current NRTI toxicity	**39 (29.3)**	**12 (52.1)**	**16 (21.3)**	**1 (20.0)**	**10 (33.3)**
TDF renal	18	3	8	0	7
Peripheral neuropathy	4	2	2	0	0
lipoatrophy	3	2	1	0	0
other	14	5	5	1	3
Intensify PI monotherapy	15 (11.3)	1 (4.3)	3 (4.0)	0 (0)	11 (36.7)
Viral failure	10	1	2	0	7
Paradigm change	4	0	1	0	3
Symptoms	1	0	0	0	1
Other	42 (30.8)	6 (26.1)	25 (33.3)	2 (40.0)	8 (26.7)
Resistance	6	0	2	0	4
Rationalise PI/r+NNRTI+NRTI	5	1	4	0	0
Efavirenz toxicity	4	0	4	0	0
Prior NRTI toxicity	2	0	2	0	0
Viral failure	3	0	2	0	1
Rationalise for planned pregnancy	2	1	1	0	0
Renal impairment	2	0	2	0	0
Other	8	1	3	1	3
Not documented	10	3	5	2	0

Figure 1: Cumulative total number prescribed PIDAT regimens

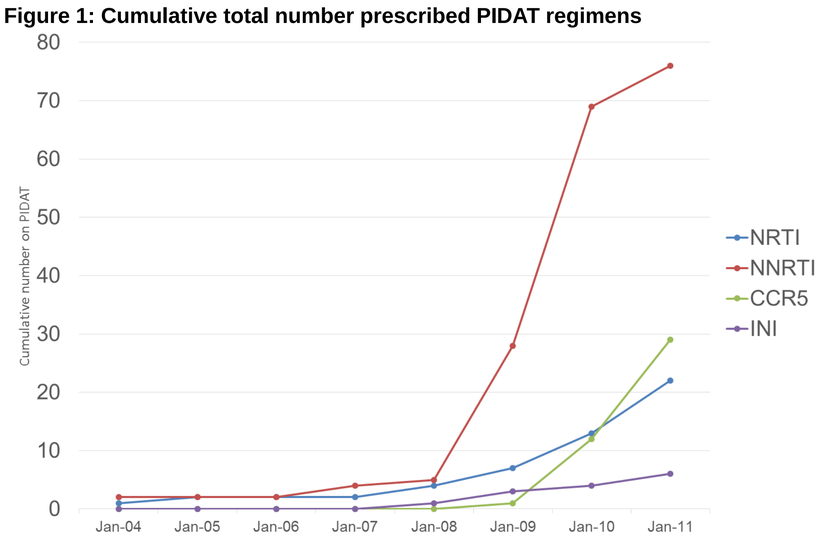


Table 4: Specific PIDAT regimens switch to

	Protease inhibitor used				
Regimen type	Total	DRV/r	LPV/r	ATV/r	Other
N	133	109	11	10	3
PI/r+NRTI	23 (17.3)	13 (11.8)	6 (55)	2 (22)	2 (25)
TDF	11	7	2	1	1
ABC	2	2	0	0	0
3TC/FTC	10	4	4	1	1
PI/r+NNRTI	75 (56.4)	68 (62)	3 (27.3)	4 (44)	0 (0)
EFV	2	0	1	1	0
ETR OD	47	47	0	0	0
ETR BD>OD	8	8	0	0	0
ETR BD	12	12	0	0	0
NVP	6	1	2	3	0
PI/r+INI	5 (3.8)	4 (3.6)	0 (0)	1 (25)	0 (0)
RAL	5	4	0	1	0
PI/r+CCR5-A	30 (22.6)	24 (21.8)	2 (18)	3 (33)	1 (25)
MVC OD	23	19	1	3	0
MVC BD>OD	1	1	0	0	0
MVC BD	6	4	1	0	1

BD>OD: Switch to once daily dosing after starting PIDAT

Figure 2: 96 and 144 week snapshot analysis (+/-10weeks), switch ignored

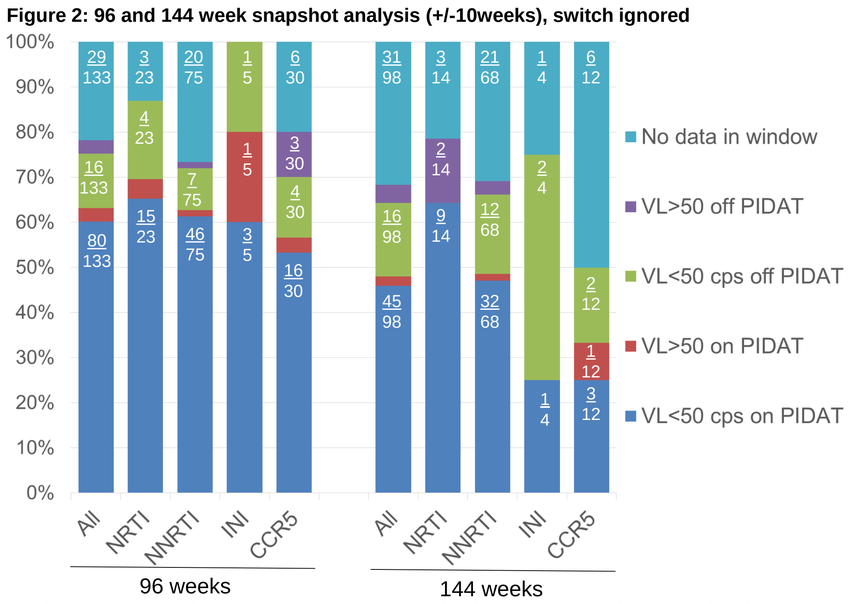


Table 5: 48, 96 and 144 week snapshot analysis (+/-10weeks) of viral load outcomes according to regimen status (n/N [%])

Week (+/-10)	Analysis	All	NRTI	NNRTI	INI	CCR5-A
48	ITT, M=F, S=F	85/133 (63.9)	16/23 (69.6)	50/75 (66.7)	1/5 (20.0)	18/30 (60.0)
	ITT, M=F, S=I	98/133 (73.7)	16/23 (69.6)	58/75 (77.3)	2/5 (40.0)	22/30 (73.3)
	OT, M=E	85/95 (89.5)	16/16 (100.0)	50/55 (90.0)	1/4 (25.0)	18/20 (90.0)
96	ITT, M=F, S=F	80/133 (60.2)	15/23 (65.2)	46/75 (61.3)	3/5 (60.0)	16/30 (53.3)
	ITT, M=F, S=I	96/133 (72.2)	19/23 (82.6)	53/75 (70.7)	4/5 (80.0)	20/30 (66.7)
	OT, M=E	80/84 (95.2)	15/16 (93.8)	46/47 (97.9)	3/4 (75.0)	16/17 (94.1)
144	ITT, M=F, S=F	45/98 (45.9)	9/14 (64.3)	32/68 (47.1)	1/4 (25.0)	3/12 (25.0)
	ITT, M=F, S=I	61/98 (62.2)	9/14 (64.3)	44/68 (64.7)	3/4 (75.0)	5/12 (41.7)
	OT, M=E	45/47 (95.7)	9/9 (100.0)	32/33 (97.0)	1/1 (100.0)	3/4 (75.0)

S=F (switch=fail): any change in PIDAT regimen, including substation of drugs
S=F: swicth=failure; M=E: missing excluded

Results (3)

Change of ART whilst maintaining PIDAT

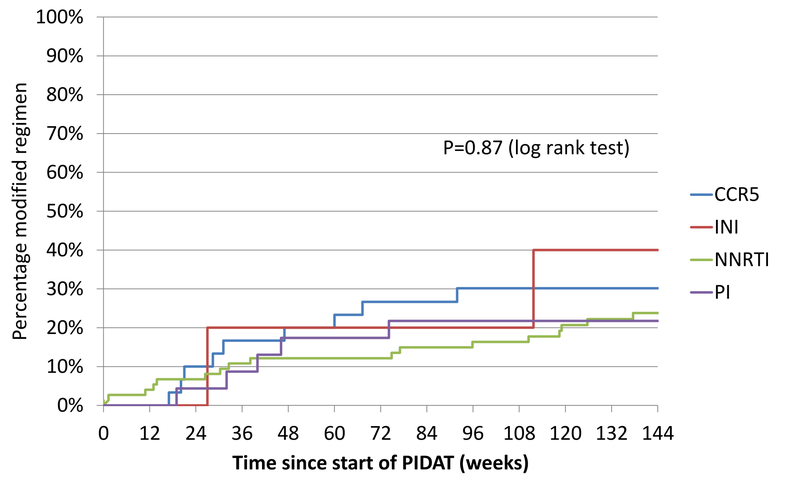
- 12% (17/133) change one or more components of their PIDAT regimen. 41% (7/17) made a change in PI/r, 76% (13/17) changed the non-PI component, 84% (11/13) within class, mainly etravirine to rilpivirine due to pill burden (7/11).
- Outcomes of any switch equals fail analysis shown in table 5.

Table 6: Discontinuations from PIDAT

	Numbers stopping according to regimen (N [%])				
Outcomes	Total	NRTI	NNRTI	INI	CCR5-A
Discontinued PIDAT	32 (24)	7 (31.8%)	13 (17.1%)	3 (50)	9 (31)
Weeks till stop PIDAT, median (range)	-	60 (36, 180)	110 (30, 179)	111 (27, 240)	31 (21, 60)
Viral failure	6	1	1	0	4
VF (Adherence)	4	1	1	1	1
Toxicity	6	0	4	0	2
Switch to PI/r monotherapy	2[b]	0	2[b]	0	0
Other	14	5	5	2	2

a - Follow up (FU): M=F, discontinuation prior to time point=F, excludes insufficient FU at time point.
b - 6 patients switched to PI monotherapy, 4 due to toxicity, 2 for simplification

Figure 2: Kaplan-Meier plot of time to discontinuation of each PIDAT regimen



Discussion

- In the main PIDAT is being utilised for a selected group of patients who are virologically suppressed with good CD4 counts and have extensive prior ART exposure, but not necessarily extensive resistance (table 1).
- There are a wide range of indications for switching to PIDAT, however 29% (39/133) of the defined indications related to ART toxicity.
- Dual-PI based cART was the most common prior regimen (table 2), and likely reflects local prior prescribing practices.
- Although etravirine/darunavir/r was the most prevalent PIDAT regimen over the past 7 years (57%), the use of maraviroc has increased significantly since 2009.
- Maraviroc usage is likely driven by use of genotypic tropism determination, increasing experience with once daily dosing, and lower pill burden compared to other PIDAT regimens.
- When switching to PIDAT due to viral failure on PI-monotherapy, 7/10 had VL<400c/ml.
- Virological outcomes are difficult to interpret in selected populations in clinical practice due to missing data.

Limitations

- Retrospective medical notes-based audit
- Relatively small numbers of patients.
- Different PIDAT regimens may not be comparable.

Conclusions

- Indications for PIDAT within our cohort were predominantly rationalisation of more complex regimens, or as a TDF-sparing strategy after renal impairment.
- Longer term outcomes in this selected population appear positive, however prospective clinical trials are required using specific PIDAT regimens in a switch study are required.