15th Residential Course on Clinical Pharmacology of Antiretrovirals

MANAGEMENT OF POLYPHARMACY AND DDIs
A case-based discussion

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Turin, 15 January 2019

INTRODUCTION

- An estimated **37,9 million** people are living with HIV globally. *WHO 2018*
- Improvements in the diagnosis and management of the disease, associated with the effectiveness of ART, have led to a life expectancy close to that of HIV-negative individuals → HIV chronic disease
- It is estimated that by 2030 nearly three-quarters of PLWH will be 50 years and older →Early aging → comorbidity → polypharmacy → DDIs
- 31% of deaths are attributed to **CVD**, making it the leading co-morbidity for PLWH. (Taylor KA et al, 2019)
- People living with HIV are twice as likely to develop CVD (**RR:2,16** - 95% CI, 1,68-2,77) (Shah et al, 2018)

HIV as ***major CV risk factor*** (Hsue et al, 2018)

Analysis of the Efficacy and Pharmacological interaction between antiplatelet therapy and antiretroviral therapy in the clinical setting

	(n=32)
Age (yrs)	61,03 ± 9,01
Gender M	27 (84%)
Smokers	18 (56%)
Substance Abuse	16 (50%)
Hypertension	19 (59%)
Family history of CVD	11 (34%)
Diabetes mellitus type 2 (DMT2)	4 (12%)
DMT2 on insulin therapy	1 (3%)
Dislypidemia	24 (75%)
Chronic kidney failure (CKD)	10 (31%)
Chronic heart failure	2 (6%)
Peripheral arterial disease	13 (40%)
HCV coinfection	7 (22%)
HBV coinfection	2 (6%)

Variables linked with HIV	(n=32)
Nadir CD4+	172,1 ± 128,80
Undetectable Viral Load (VL<20cp)	31 (97%)
Time on ARVs (yrs)	16,56 ± 6,01
Time with undetectable VL (yrs)	8 ± 5,49
On PI	12 (38%)
On NRTIs	23 (72%)
On NNRTIs	10 (31%)
On INSTI	18 (56%)
On CCR5i	2 (6%)
ddI/d4T/IDV experienced	18 (56%)

Most prescribed HAART : 12 (37%) → 2NRTIs + INSTI

Unpublished data

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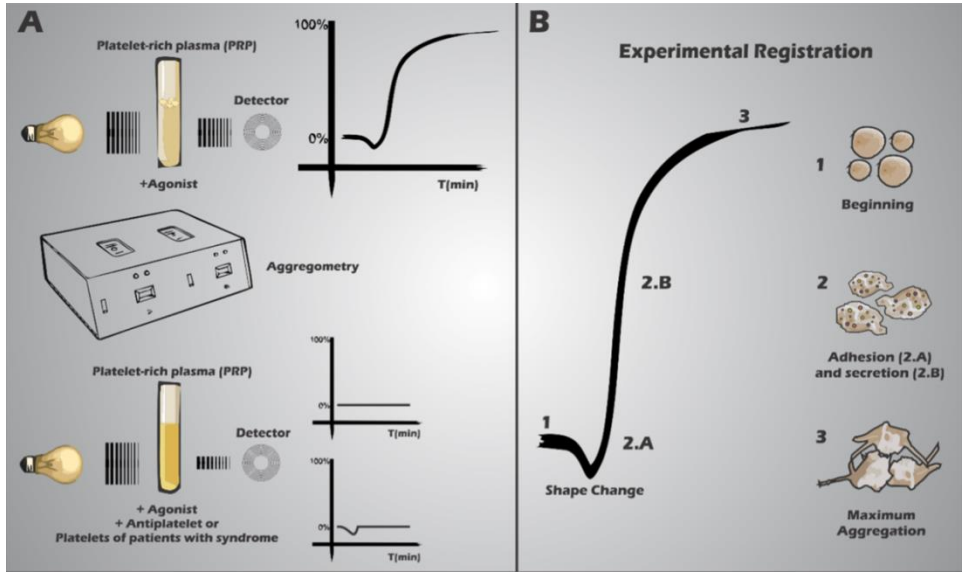
Acute CV event	(n=26)
Age (yrs)	60,73 ± 8,92
Unstable angina	11 (42%)
NSTEMI	3 (11%)
STEMI	9 (35%)
Other	3 (12%)
CD4+ during the event	545,67 ± 265,40
% CD4+ during the event	28,29 ± 10,12
CD4+ after the event	561,26 ± 301,17
% CD4+ after the event	25,75 ± 8,76

Antiplatelet Therapy	(n=32)
ASA	9
Clopidogrel	4
ASA + Ticlopidine	1
ASA + Clopidogrel	9
ASA + Prasugrel	5
ASA + Ticagrelor	4

Unpublished data

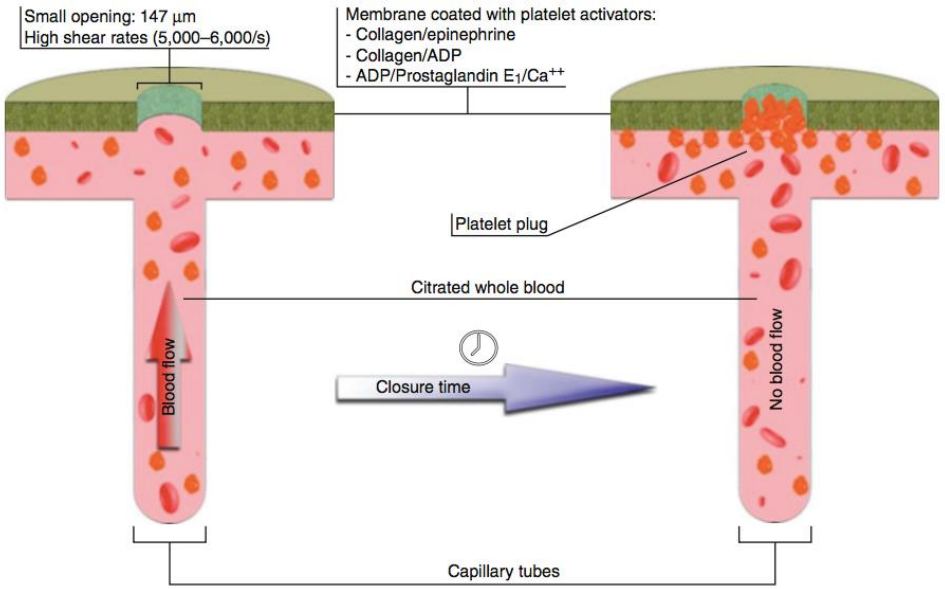
TECHNIQUES OF PLATELET AGGREGOMETRY

Light Transmission [Born] Aggregometry (LTA)



The historical "gold standard", turbidometric platelet aggregometry which measures platelet aggregation in PRP (platelet-rich plasma), it is based on the detection of difference in light transmission by a photometer after adding a platelet agonist to PRP → **ADP** or **Arachidonic Acid (AA)**. Result expressed as **%**

PFA 200 (INNOVANCE® PFA P2Y)



Platelet Function Analyzer

(PFA-100 for monitoring aspirin and Innovance PFA-200→ PFA P2Y ADP/PGE1/Ca^2 for thienopyridines) It is a simple, rapid, point-of-care whole blood method, low sample volumes and no sample preparation

Result expressed in sec

Koltai K et al. Platelet Aggregometry Testing: Molecular Mechanisms, Techniques and Clinical Implications. Int J Mol Sci. 2017 Aug; 18(8): 1803

Pt	Antiplatelet therapy	LTA AA (500 μg/ml) % nv >65-90	LTA ADP (10 μM/L) % nv> 60-90	PFA200 CT (s) nv<106	HAART
1	ASA	70	88	-	ABC/3TC + DTG
2	ASA	4	53	-	ABC/3TC + NVP
3	ASA	0	46	-	ABC/3TC/DTG
4	ASA	0	41	-	ABC/3TC/DTG
5	ASA	4	63	-	DRV/c + ABC/3TC
6	ASA	0	49	-	DRV/r + 3TC
7	ASA	4	18	-	DRV/r + DTG
8	ASA	8	81	-	RAL + DRV + RTV + ETV
9	ASA	10	61	-	TDF/FTC + NVP
10	ASA + Clopidogrel	0	27	-	ABC/3TC + ETR
11	ASA + Clopidogrel	0	38	-	ABC/3TC/DTG
12	ASA + Clopidogrel	87	52	80	DRV/r + MVC
13	ASA + Clopidogrel	10	37	-	TAF/FTC + RAL
14	ASA + Clopidogrel	4	23	-	TAF/FTC + RAL
15	ASA + Clopidogrel	0	25	>300	TAF/FTC + RAL
16	ASA + Clopidogrel	-	-	>300	TDF/FTC + DRV/R

effective antiplatelet activity

borderline antiplatelet activity

poor antiplatelet activity

Pt	Antiplatelet therapy	LTA AA (500 μg/ml) % nv>65-90	LTA ADP (10 μM/L) % nv>60-90	PFA200 CT (s) nv<106	HAART
17	ASA + Clopidogrel	0	6	>300	TDF/FTC/RPV
18	ASA + Clopidogrel	0	3	-	TDF/FTC + ATV/c
19	ASA + Prasugrel	5	0	140	ABC/3TC/DTG
20	ASA + Prasugrel	7	6	>300	DRV + RTV + ETR
21	ASA + Prasugrel	6	6	>300	DRV + RTV + ETV + MVC + ENF
22	ASA + Prasugrel	0	0	>300	DRV+ RTV + RAL
23	ASA + Prasugrel	0	0	>300	DTG + RPV
24	ASA + Ticagrelor	0	10	>300	3TC + MVC + DTG
25	ASA + Ticagrelor	0	5	>300	ABC/3TC/DTG
26	ASA + Ticagrelor	4	6	>300	DTG + RPV
27	ASA + Ticagrelor	0	0	234	TAF/FTC/RPV
28	ASA + Ticlopidine	82	83	74	DRV + RTV + 3TC + DDI + ENF
29	Clopidogrel	91	51	-	ABC/3TC + RAL
30	Clopidogrel	69	74	80	ABC/3TC + RAL
31	Clopidogrel	63	20	>300	TAF/FTC + DTG
32	Clopidogrel	70	75	191	DRV/c

effective antiplatelet activity

borderline antiplatelet activity

poor antiplatelet activity

Analysis of the Efficacy and Pharmacological interaction between antiplatelet therapy and antiretroviral therapy in the clinical setting

Platelet Aggregation	(n=32)
Inhibited	26 (81%)
Normal	6 (19%)

Boosted PI (3)

Abacavir (3)

Platelet Aggregation	No PI ± booster and No ABC (n=10)
Inhibited	10 (100%)
Normal	0 (0%)

Analysis of the Efficacy and Pharmacological interaction between antiplatelet therapy and antiretroviral therapy in the clinical setting

Platelet Aggregation	PI ± booster (n=12)	No PI (n=20)
Inhibited	9 (75%)	17 (85%)
Normal	3 (25%)	3 (15%)

Platelet Aggregation	boosted PI+ Ticlopidine or Clopidogrel (n=5)
Inhibited	2 (40%)
Normal	3 (60%)

PI

Pharmacokinetic interactions

PRASUGREL is a prodrug and is converted to its active metabolite mainly by CYP 3A4 and CYP 2B6. Pharmacoenhancer like ritonavir and cobicistat decreased the AUC and Cmax of prasugrel active metabolite without impairing prasugrel antiplatelet effect.

CLOPIDOGREL is a prodrug and is converted to its active metabolite via CYP 3A4, 2B6, 2C19 and 1A2. The effect of induction of CYP 2C19 and inhibition of CYP 3A4 by boosted PIs decreases exposure of the active metabolite leading to non-responsiveness to clopidogrel.

TICAGRELOR undergoes extensive CYP 3A4 metabolism. Strong inhibitors of CYP 3A4 may lead to a substantial increase in exposure to ticagrelor and bleeding risk.

HIV Drug Interactions

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CLINICAL SETTING: HAART switch

PI

MI

Test	HAART	Antiplatelet therapy	PFA200 (s) nv<106	% aggregation ADP (10 μM/l) nv> 60-90	% aggregation AA (500 μg/ml) nv>65-90
1	DRV/R + MVC	ASA + Clopidogrel	80s	52%	87%
2	RAL+TAF/FTC	ASA + Clopidogrel	>300s	0%	0%

PAD

Test	HAART	Antiplatelet therapy	PFA200 (s) nv<106	% aggregation ADP (10 μM/l) nv> 60-90	% aggregation AA (500 μg/ml) nv>65-90
1	DRV/cobi	Clopidogrel	191s	75%	70%
2	DTG+3TC	Clopidogrel	>300s	0%	0%

- Same comedications remained unchanged before and after ARV switch
- Self-reported adherence to all drugs was 100%

PAD: peripheral arterial disease MI: myocardial infarction

Analysis of the Efficacy and Pharmacological interaction between antiplatelet therapy and antiretroviral therapy in the clinical setting

Platelet Aggregation	ABC (n=11)	No ABC (n=21)
Inhibited	8 (73%)	18 (86%)
Normal	3 (27%)	3 (14%)

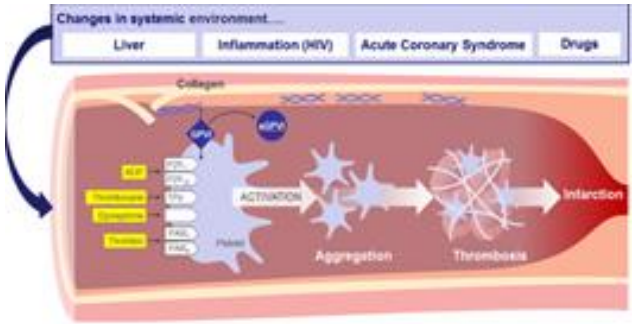
ABC

Pharmacodynamic Interactions

ABC → **PLTS**

CROI
Conference on Retroviruses and Opportunistic Infections

- **Platelet (PLT) dysfunction and activation[1-3]**
- **Endothelial inflammation and leukocyte recruitment[4-5]**



1. Mallon P, et al. CROI 2018. Boston, MA. Oral 80
2. Mallon P, et al. CROI 2018. Boston, MA. Poster 677LB
3. Taylor K, et al. CROI 2018. Boston, MA. Poster 673
4. Collado-Diaz V, et al. CROI 2018. Boston, MA. Poster 674
5. Andujar I, et al. CROI 2017. Seattle, WA. Poster 609
6. Collado-Diaz V, et al. EACS 2017. Milan, Italy. Poster 2-7

HIV Drug Interactions

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Potential Interaction

Abacavir (ABC)

Clopidogrel

Quality of Evidence: Very Low

Summary:

Coadministration has not been studied. Clopidogrel is a prodrug that is converted to its active metabolites via CYPs 3A4, 2B6, 2C19 and 1A2 and therefore no pharmacokinetic interaction is expected with abacavir. However, abacavir has been shown to potentiate platelet activation in vitro and thereby may reduce the pharmacodynamic effect of clopidogrel. An alternative NRTI or antiplatelet agent should be considered.

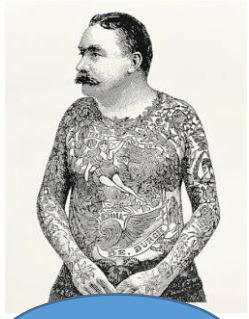
Description:

Platelets were isolated from healthy, HIV-negative, donors and aggregation assessed in the presence of abacavir, tenofovir-DF (TDF) or tenofovir alafenamide (TAF). Abacavir significantly enhanced expression of platelet activation markers whereas TAF and TDF had no effect. These increases in the presence of abacavir demonstrate increased degranulation, indicating enhanced platelet activation and potentially a pro-thrombotic impact. Studies in mice showed normal platelet aggregation responses in the presence of TAF or TDF, whereas abacavir potentiated aggregation, again indicative of a pro-thrombotic effect.

Comparative impact of antiretrovirals on human platelet activation. Taylor K, Rauzi F, Smyth E, et al. Conference on Retroviruses and Opportunistic Infections (CROI), Boston, March 2018, abstract 673.

CLINICAL SETTING: HAART switch

ABC



PAD

Test	HAART	Antiplatelet therapy	PFA200 (s) nv<106	% aggregation ADP (10 μM/l) nv> 60-90	% aggregation AA (500 μg/ml) nv>65-90
1	ABC/3TC + RAL	Clopidogrel	80s	74%	69%
2	TAF/FTC + RAL	Clopidogrel	>300s	23%	0%

PAD

Test	HAART	Antiplatelet therapy	PFA200 (s) nv<106	% aggregation ADP (10 μM/l) nv> 60-90	% aggregation AA (500 μg/ml) nv>65-90
1	ABC/3TC + DTG	ASA	-	88%	70%
2	TAF/FTC + RAL	ASA + Clopidogrel	75s	55%	0%

- Same comedications remained unchanged before and after ARV switch
- Self-reported adherence to all drugs was 100%

PAD: peripheral arterial disease

But what happens in a patient treated with clopidogrel and protease inhibitor used for anti-HCV Tx ???

- Glecaprevir is a direct acting antiviral agent and HCV NS3/4A protease inhibitor, available as an oral fixed-dose combination therapy with pibrentasvir (NS5A inhibitor), named Maviret.
- Glecaprevir is a inhibitor of: cytochrome P450 3A, UDP-glucuronosyltransferase 1-1, P-gp1, ATP-binding cassette G2,OATP1 B1/3
- Most important interactions due to its inhibitory activity are with:
  - ✓ Atorvastatin, simvastatin, lovastatin (OATP1B1/3, P-gp and BCRP+ CYP3A for atorvastatin)
  - ✓ Dabigatran (P-gp)
  - ✓ Ethinylestradiol-containing products (OATP)
  - ✓ Vimblastine, vincristine (P-gp)

HEP Drug Interactions

DRUGBANK

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B.A.

CLINICAL CASE

- 56 yo Caucasian male
- History of previous IVDA
- Heavy smoker
- Arterial hypertension since 2000
- COPD
- HIV+ since 1986 /HCV+ since 1994 (genotype 2)
- CD4 Nadir : 55 cell/µl, 5%, ratio 0.1 set point HIV-RNA: 69000 cp/ml

Timing	ARV	Switch for
01/93-06/93	AZT	Side effects
02/94-06/95	ddI	Side effects
06/95-08/95	AZT	Intolerance
08/96-11/96	ddC	Toxicity
11/96-12/96	3TC	Vir. Failure
12/96-03/97	3TC+SQV	Vir. Failure
03/97-07/98	3TC+SQV+d4T	Vir. Failure

Timing	ARV	Switch for
07/98-05/01	3TC+IDV+d4T	Vir. Failure
05/01-06/01	AZT/3TC/ABC+NVP	Intolerance
06/01-03/03	ABC+ddI+NVP	Vir. Failure
03/03-06/06	TDF+ddI+LPV/rtv	Simplification
06/06-03/13	TDF/FTC+LPV/rtv	Simplification
03/13-10/16	TDF/FTC+DRV/rtv	DD Interactions
10/16-06/17	TDF/FTC+RAL	TAF availability

B.A.

CLINICAL CASE

Cardiovascular history

- 2002 (38yo) CAD: PTCA and stenting of LAD
- 2007: NSTEMI → DES of RCA and OM
- 2017: thoracic pain and in-stent restenosis
  →PTCA + DES of CT-LAD, DES of RCA POBA of Cx
- March 2018: unstable angina and in-stent restenosis
  →PEB of Cx and POBA of CT

RAL 400 bid + TAF/FTC

HIV-RNA: undetectable
CD4 T cell: 540/µl, 20%, r 0.3

CONCOMITANT MEDICATIONS	
Methadone 100 mg	Ivabradine
Acetylsalicylic acid	Paroxetine
Clopidogrel	Pravastatin 20 mg
Pantoprazole 20 mg	Tiotropium bromide
bisoprolol	nitroglycerine

May 2018 : PLATELET AGGREGATION TEST

LTA ADP 10 µM	PFA 200	% aggregation AA
21%	>300s	0%

B.A.

CLINICAL CASE

HCV-RNA: 6180000 UI/ml gen 2, treatment naïve
2019 Transient elastography: Stiffness: 6.9 KPa ; CAP 330 dB/m
30/Sep/2019: start GLE/PIB for 8 w

QUESTION: IS CLOPIDOGREL FULLY EFFECTIVE with G/P?

HEP Drug Interactions

Coadministration has not been studied but based on metabolism and clearance
a clinically significant interaction is unlikely

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PLATELET AGGREGATION & FUNCTION TEST

	HAART	LTA (final aggregation)* ADP 10 µM	PFA 200 -P2Y12** Closure Time	% aggregation AA (500 µg/ml)
BL	RAL 400 BID+ TAF/FTC	30 %	>300 sec	0%
W 2 G/P	RAL 400 BID+ TAF/FTC	4 %	>300 sec	4%

CLOPIDOGREL WORKS !

*normal value: > 60 %

**normal value: <106 sec

EOT: HCV-RNA =0

CONCLUSIONS

- Several PK and PD factors can influence antiplatelet treatment (APT) with different clinical outcome.
- Coadministration of clopidogrel and ticagrelor with strong inhibitors or strong inducers of CYP3A4 is contraindicated, whereas prasugrel is safe with any ARV combination.
- Abacavir was related to high cardiovascular risk in HIV + patients, which mechanisms are not fully elucidated, however there is an increase number of reports of heightened platelet reactivity (HPR) as key factor.
- Glecaprevir is only a weak inhibitor of CYP3A4 and is unlikely to affect the exposure of clopidogrel to any clinically significant extent.
- The assessment of residual platelet function in HIV patients in secondary prevention for CV events deserves more attention as a clinical option to prevent recurrences in such high CV risk population.
- Rapid and simple methods, like PFA, can be used to measure platelet function during APT and, even if not fully validated in this population, may guide the management in complex patients.

Acknowledgements

Unit of Infectious Diseases

Prof. Giovanni Di Perri
Prof. Stefano Bonora
Mariacristina Tettoni
Andrea Calcagno
Micol Ferrara
Alessandro Duchi
Laura Trentini
Filippo Lipani
Letizia Marinaro
Alessandro Lazzaro
Stefano Biffi
Mattia Trunfio
Alessandro Di Stefano
Chiara Montrucchio

Clin. Pharm. Lab.

Antonio D'Avolio
Mauro Sciandra
Jessica Cusato
Amedeo De Nicolò

Hematology Lab.

Alessandra Valpreda

Mol. Biol. Lab.

Valeria Ghisetti
Tiziano Allice
Elisa Burdino
Maria Grazia Milia