Tops & Flops

Agata Skrzat-Klapaczyńska

Hospital for Infectious Diseases, Department for Adult's Infectious Diseases

Medical University of Warsaw, Poland

Conflict of interest

I have no conflict of interest

Unintended pregnancy

- General population - in 2012, 213 million pregnancies occurred worldwide, with an estimated 85 million classified as unintended[1]
- Up to 85% pregnancies in HIV+ women reported as being „unplanned"[2,3]
- Pregnancy outcomes of HIV+ in a district general hospital in London (2008 – 2014); 137 pregnancies; most (60%, 63/105) were unplanned[4]

(1) Sedgh G *et al., Stud Fam Plann.* 2014 Sep;45(3):301-14
(2) Loutfy M *et al., HIV Med.* 2012 Feb;13(2):107-17
(3) Sutton *et al.*, CROI 2012
(4) Carey L *et al. J Obstet Gynaecol.* 2018 Mar 12:1-4

Drug-drug Interactions between Contraceptives/Hormone Replacement Therapy and ARVs

		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
Es	ethinylestradiol (COC, TS, VR)	↔	↓19%[a]	↓30%	↓44%[b]	↓42%[b]	↔[c]	↑22%	↓20%	↑14%	↔	↑3%	↓25%[d]	↔	↔	↔	↔	↔	↔	↔
Progestins	desogestrel (COC)	↑	↑[e,a]	↑	↑[f]	↑[f]	↓[g]	↓	↓	↔	↔	↔	↑[d,e]	↔	↔	↔	↔	↔	↔	↔
	desogestrel (POP)	↑	↑	↑	↑	↑	↓[g]	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	drospirenone (COC)	↑	↑[e,a]	↑[f]	↑[f]	↑[f]	↓[g]	↓	↓	↔	↔	↔	↑[d,e]	↔	↔	↔	↔	↔	↔	↔
	etonogestrel (IP)	↑	↑	↑	↑	↑52%	↓63%[g]	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	etonogestrel (VR)	↑	↑[h]	↑	↑[h]	↑[h]	↓[g]	↓	↓	↔	↔	↔	↑[h]	↔	↔	↔	↔	↔	↔	↔
	gestodene (COC)	↑	↑[e,a]	↑	↑[f]	↑[f]	↓[g]	↓	↓	↔	↔	↔	↑[d,e]	↔	↔	↔	↔	↔	↔	↔
	levonorgestrel (COC)	↑	↑[e,a]	↑	↑[f]	↑[f]	↓[g]	↓	↑	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	levonorgestrel (IP)	↑	↑	↑	↑	↑	↓47%[g]	↓	↑14%	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	levonorgestrel (POP)	↑	↑	↑	↑	↑	↓[g]	↓	↑	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	levonorgestrel (IUD)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	medroxyprogesterone (POI)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	norelgestromin (TS)	↑	↑[e,a]	↑	↑[f]	↑83%[f]	↓[g]	↓	↓	↔	↔	↔	↑[d,e]	↔	↔	↔	↔	↔	↔	↔
	norethisterone (COC)	↑	↑[e,a,i]	↑	↓14%[f]	↓17%[f]	↓[g]	↓5%	↓19%	↓11%	↔	↔	↑[d,e]	↔	↔	↔	↔	↔	↔	↔
	norethisterone (POI)	↔	↔	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	norethisterone (POP)	↑	↑50%	↑	↑50%	↑50%	↓[g]	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	norgestimate (COC)	↑	↑85%[e,a]	↑	↑[f]	↑[f]	↓64%[g]	↓	↓	↔	↔	↔	↑126%[d,e]	↑14%	↔	↔	↔	↔	↔	↔
	norgestrel (COC)	↑	↑[e,a]	↑	↑[f]	↑[f]	↓[g]	↓	↑	↔	↔	↔	↑[d,e]	↔	↔	↔	↔	↔	↔	↔
Other	levonorgestrel (EC)	↑[j]	↑[j]	↑[j]	↑[j]	↑[j]	↓58%[k]	↔	↔	↔	↔	↔	↑[j]	↔	↔	↔	↔	↔	↔	↔
	mifepristone	↑[j]	↑[j]	↑[j]	↑[j]	↑[j]	↓	↓	↓	E[j]	E[j]	↔	↑[j]	↔	↔	↔	↔	↔	↔	↔
	ulipristal	↑[j]	↑[j]	↑[j]	↑[j]	↑[j]	↓[j]	↓[j]	↓[j]	↔	↔	↔	↑[j]	↔	↔	↔	↔	↔	↔	↔

Legend

↑ potential increased exposure of the hormone
↓ potential decreased exposure of the hormone
↔ no significant effect
D potential decreased exposure of ARV drug
E potential elevated exposure of ARV drug
ATV/c ATV co-formulated with COBI (300/150 mg qd);
DRV/c DRV co-formulated with COBI (800/150 mg qd)
a unboosted ATV increased ethinylestradiol AUC by 48%. Use no more

Colour legend

no clinically significant interaction expected
these drugs should not be co-administered
potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
potential interaction likely to be of weak intensity or unlikely to impair contraceptive efficacy. Additional action/monitoring or dosage adjustment is unlikely to be required

EACS guidelines 2017

Drug interactions between hormonal contraceptives and antiretrovirals

Kavita Nanda[a], Gretchen S. Stuart[b], Jennifer Robinson[c], Andrew L. Gray[d], Naomi K. Tepper[e] and Mary E. Gaffield[f]

- 46 studies (systematic review)
- Hormonal contraceptives
  - Combined oral contraceptives
  - Progestin-only pills
  - Emergency contraceptive pills
  - Injectables
  - Vaginal rings
  - Patches
  - Implants
- Studies included women - HIV-positive, HIV-negative but at risk of HIV, or healthy, who concurrently used cART, PrEP or single antiretrovirals and hormonal contraceptives

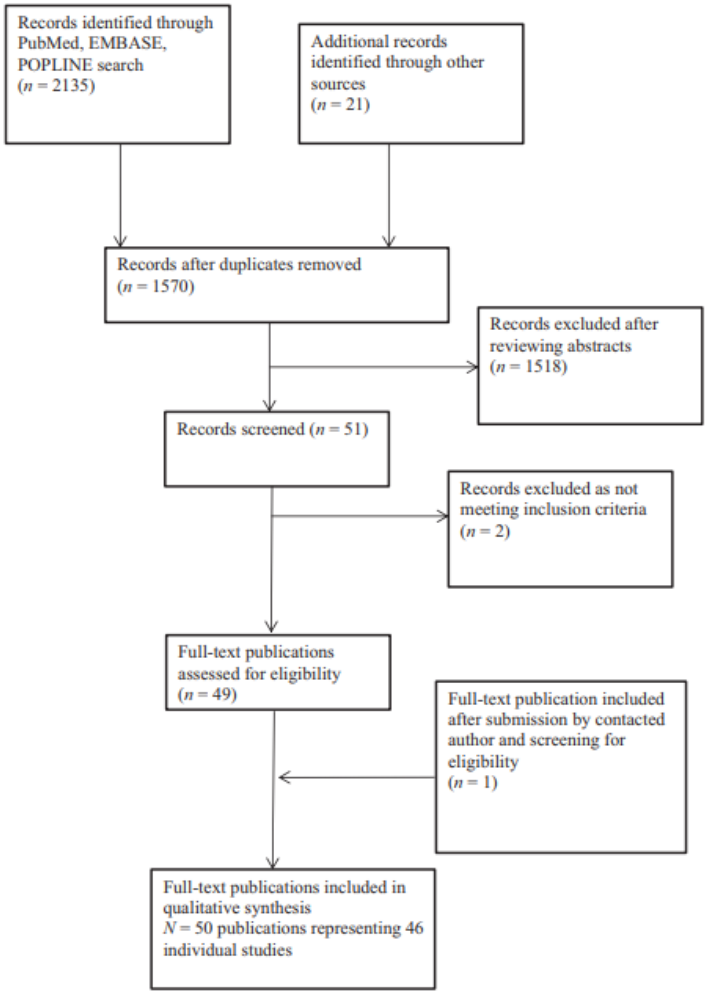


Fig. 1. Flow diagram of publication selection for inclusion into the review.

Nanda K *et al. AIDS.* 2017 Apr 24;31(7):917-952

Results

- Antiretroviral plasma concentrations and effectiveness are generally not affected by hormonal contraceptives
- Most antiretrovirals whether used for therapy or prevention, have limited interactions with hormonal contraceptive methods, with the exception of efavirenz
- Implants remain very effective despite drug interactions

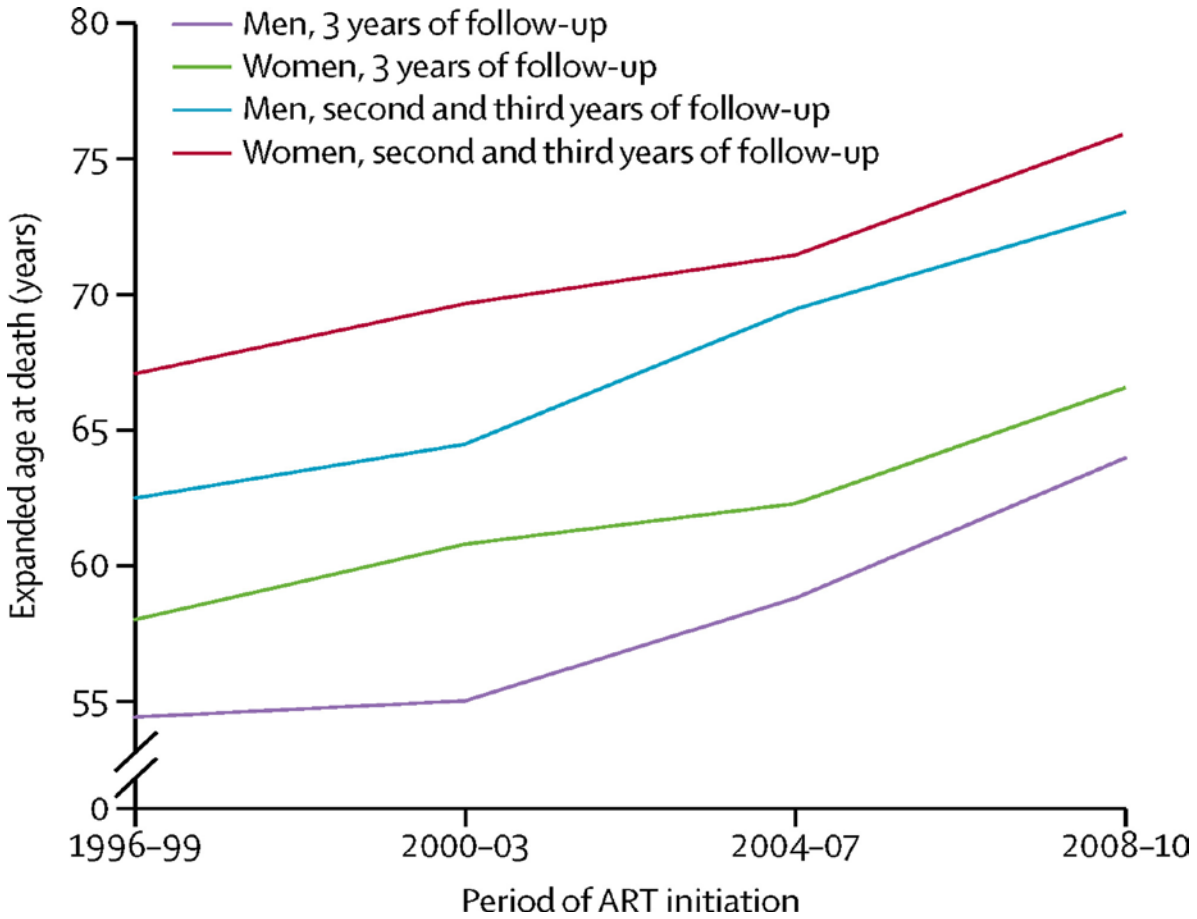
Conclusion

- Women taking antiretrovirals, for treatment or prevention, should not be denied access to the full range of hormonal contraceptive options

- The changing tides of antiretroviral treatment we should consider adjusting antiretroviral regimen to the contraceptive method, not the other way around

Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies

The Antiretroviral Therapy Cohort Collaboration



Antiretroviral Therapy Cohort Collaboration, *Lancet HIV.* 2017 Aug;4(8):e349-e356

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention

M.G. Fowler, M. Qin, S.A. Fiscus, J.S. Currier, P.M. Flynn, T. Chipato, J. McIntyre, D. Gnanashanmugam, G.K. Siberry, A.S. Coletti, T.E. Taha, K.L. Klingman, F.E. Martinson, M. Owor, A. Violari, D. Moodley, G.B. Theron, R. Bhosale, R. Bobat, B.H. Chi, R. Strehlau, P. Mlay, A.J. Loftis, R. Browning, T. Fenton, L. Purdue, M. Basar, D.E. Shapiro, and L.M. Mofenson, for the IMPAACT 1077BF/1077FF PROMISE Study Team*

Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline

Reed A C Siemieniuk,[1] Lyubov Lytvyn,[2] Jinell Mah Ming,[3] Rhonda Marama Mullen,[4] Florence Anam,[5] Teresia Otieno,[6] Gordon H Guyatt,[1] Graham P Taylor,[7] Claudia Beltrán-Arroyave,[8] Patrick Mbah Okwen,[9] Ruth Nduati,[10] John Kinuthia,[11] Henry Namme Luma,[12] Haresh Kirpalani,[13] Arnaud Merglen,[14] Olufunmilayo A Lesi,[15] Per Olav Vandvik,[16] Thomas Agoritsas,[17] Susan Bewley[18]

Drug names

There are a large number of different antiretroviral drugs used by people with HIV. These drug names and abbreviations will be used throughout this article.

Nucleoside reverse transcriptase inhibitors (NRTIs)

- TDF Tenofovir
- FTC Emtricitabine
- AZT Zidovudine
- 3TC Lamivudine
- ABC Abacavir

Protease inhibitors (PIs)

- LPV/r Lopinavir (boosted with ritonavir)
- ATZ/r Atazanavir (boosted with ritonavir)
- DRV/r Darunavir (boosted with ritonavir)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

- EFV Efavirenz
- RPV Rilpivirine

Integrase inhibitors

- RAL Raltegravir

Summary of response:

- We do not support recommendations of "ART in pregnant women living with HIV: a clinical practice guideline" (BMJ, 11/9/17)
- Other systematic reviews and numerous observational studies show tenofovir to be safe in HIV in pregnancy
- BHIVA does agree any decision regarding ARVs should always be discussed in full with every woman
- BHIVA's recommendation remains to continue or to start tenofovir or abacavir with emtricitabine or lamivudine as a nucleoside backbone
- We do not think this data should influence use tenofovir/emtricitabine for pre-exposure prophylaxis in women of child-bearing potential

BHIVA British HIV Association

Fowler MG et al., *N Engl J Med.* 2016 Nov 3;375(18):1726-1737
Siemieniuk RAC *et al., BMJ.* 2017 Sep 11;358:j3961
Foster JR *et al., BMJ.* 2015 Feb 24;350:h998

CD32 as a marker of the latent reservoir

CD32a is a marker of a CD4 T-cell HIV reservoir harbouring replication-competent proviruses

Benjamin Descours[1]*, Gaël Petitjean[1]*, José-Luis López-Zaragoza[2,3,4], Timothée Bruel[2,5], Raoul Raffel[1], Christina Psomas[6], Jacques Reynes[6], Christine Lacabaratz[2,3,4], Yves Levy[2,3,4], Olivier Schwartz[2,5], Jean Daniel Lelievre[2,3,4] & Monsef Benkirane[1]

CD32 Expression of Different Memory T Cell Subpopulations in the Blood and Lymph Nodal Tissue of HIV Patients and Healthy Controls Correlates With Immune Activation

Melanie Wittner, MSc,† Gábor A. Dunay, MD, PhD,‡ Silke Kummer, BA,*† Maximillian Bockhorn, MD,§ Anja Hüfner, MD,* Stefan Schmiedel, MD,* Olaf Degen, MD,*† Jan van Lunzen, MD,*†|| Johanna M. Eberhard, PhD,*† and Julian Schulze zur Wiesch, MD*†*

Descours B *et al., Nature.* 2017 Mar 23;543(7646):564-567
Wittner M *et al., J Acquir Immune Defic Syndr.* 2018 Apr 1;77(4):345-349

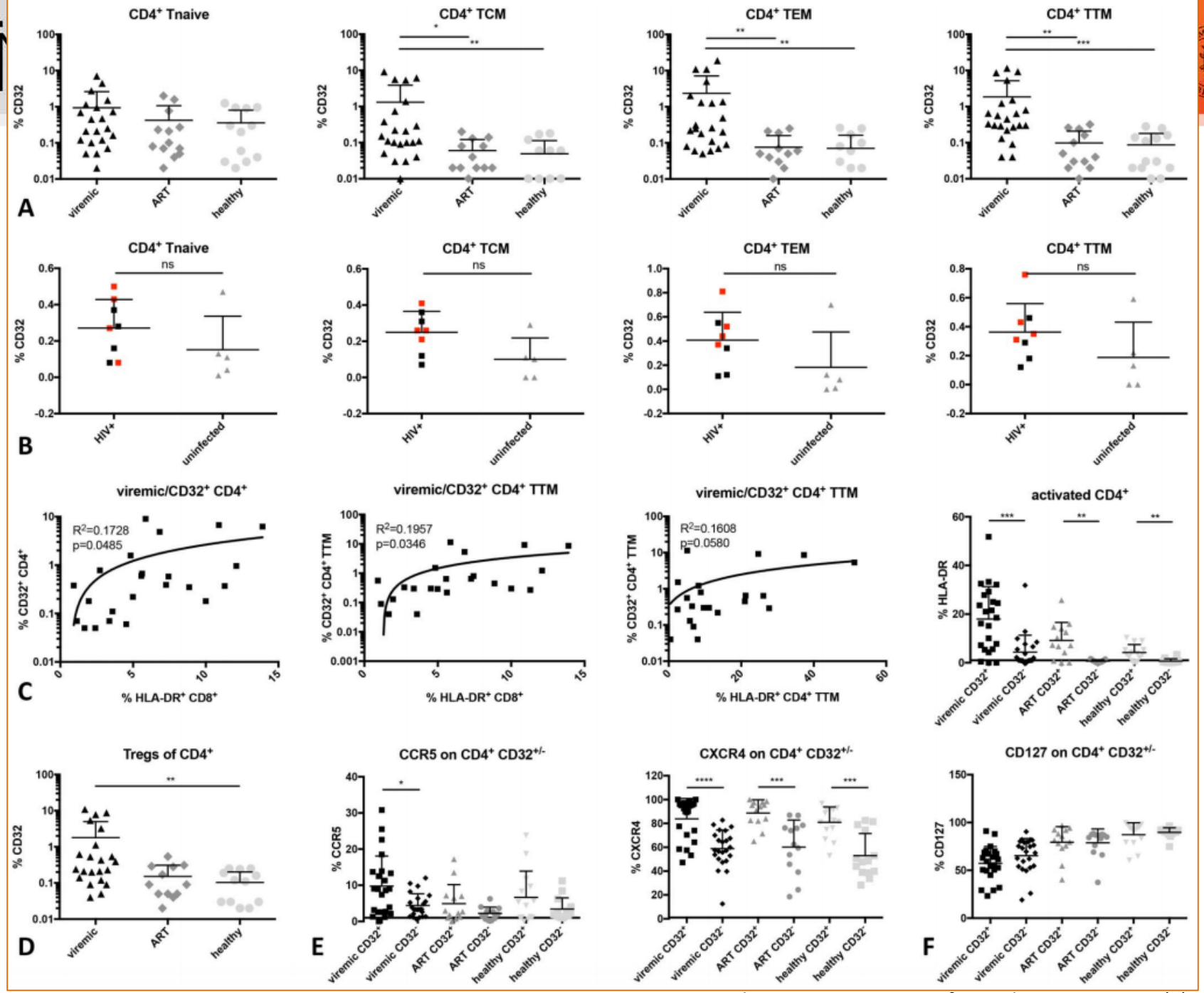
- The persistence of the HIV reservoir in infected individuals is a major obstacle to the development of a cure for HIV

- Using an *in vitro* model of HIV-infected quiescent CD4 T cells, Descours *et al.* revealed a gene expression signature of 103 upregulated genes that are specific for latently infected cells, including genes for 16 transmembrane proteins

Descours B *et al., Nature.* 2017 Mar 23;543(7646):564-567

- Descours *et al.* proved that the discovery that CD32a+ lymphocytes represent the elusive HIV-1 reservoir may lead to insights that will facilitate the specific targeting and elimination of this reservoir

Descours B *et al., Nature.* 2017 Mar 23;543(7646):564-567



Wittner M *et al., J Acquir Immune Defic Syndr.* 2018 Apr 1;77(4):345-349

- Wittner *et al.* studied peripheral blood samples of 36 HIV-1 infected patients (23 viremic patients/13 ART-treated) and healthy individuals (n = 14) as well as cells from lymph nodes (8 HIV infected, 5 controls) using a multiparametric flow cytometry panel determining surface expression of CD3, CD8,CD4, CD45RA, CCR7, CD27, CD25, CD127, CCR5, CCR6,CXCR4, CD38, HLA-DR, TIGIT and PD-1

Wittner M *et al., J Acquir Immune Defic Syndr.* 2018 Apr 1;77(4):345-349

- Expression of CD32 on total peripheral CD4+ T cells between viremic HIV patients, ART-treated and healthy individuals only differed slightly (mean values 1.501%, 0.2785% and 0.2343%, respectively)

- CD32+ levels of total CD4+ T cells or naive and memory subpopulations did not significantly differ between patients on ART and healthy, uninfected controls

Wittner M *et al., J Acquir Immune Defic Syndr.* 2018 Apr 1;77(4):345-349

Thank you

Tops & flops: hearts & heartlessness

Laura Waters
Consultant GU/HIV Medicine
CNWL, Mortimer Market Centre

Disclosures

- I have received speaker/advisory fees or conference support from Gilead, ViiV, MSD & Janssen
- I am an investigator on trials sponsored by Gilead, Janssen & Viiv

TOPS: WHERE HIV DOES NOT WORSEN OUTCOMES…

No impact of HIV *per se* on lung cancer

- Non-AIDS defining malignancies increasingly important cause of morbidity/mortality in cART era
- Several studies show higher risk lung cancer in PLHIV even after adjustment for **smoking**
- **Other possible contributors:**
  - Immune deficiency
  - History of pulmonary infection
- **Kaiser Permanente cohort analysis…**
  - 24 768 HIV+ & 257 600 HIV-, mean 4.9 & 5.8 person-years per study participant, respectively

Marcus JL *et al. AIDS.* 2017 Apr 24;31(7):989-993

Results

Smoking accounts for 94% of the population attributable fraction of lung cancer risk in PLVIH

Altekruse S *et al. AIDS.* 2018 Feb 20;32(4):513-521

For 40-year-old men with HIV, estimated cumulative lung cancer mortality for **heavy**, **moderate** & **light** **smokers** who continued to smoke was **28.9%**, **23.0%**, & **18.8%**;
for those who quit at age 40, it was **7.9%**, **6.1%** & **4.3%**; and for never smokers, it was **1.6%**

Reddy KP *et al. JAMA Intern Med.* 2017 Nov 1;177(11):1613-1621

***Demographics**: age, sex, race/ethnicity, year cohort entry; **Cancer risks**: smoking, drug/alcohol abuse, overweight/obesity*

Marcus JL *et al. AIDS.* 2017 Apr 24;31(7):989-993

No impact of well-controlled HIV on peripheral arterial disease (PAD) in VACS

- Analysis between 01/04/2003-31/12/2014
- Veterans with prevalent CVD or known PAD excluded
- Primary outcome = incident PAD events
- Results:
  - **7,708** PAD events in **91,953** people over median 9.0 years
  - After adjustment for HIV+ veterans had increased incident PAD events: **HR=1.19 [95% CI=1.13-1.25]**
  - Time-updated HIV viral load>500: **HR=1.51 [95% CI=1.38-1.65]**
  - CD4 cell counts <200: **HR=1.91 [95% CI=1.71-2.13]**
  - Time updated CD4 cell count ≥500: **HR=1.03 [95% CI=0.96-1.11]**

Beckman JA *et al. Circulation.* 2018 Mar 13

No impact of HIV on outcomes after percutaneous interventions (PCI)

- Systematic review & meta-analysis of studies on post-PCI outcome in 821 HIV+ & 1147 HIV- people

Outcomes analysed	OR (95% CI)	*p* value
Mortality	1.13 (0.65-1.96)	0.66
Cardiac Death	1.16 (0.50-2.68)	0.74
Recurrent MI	1.32 (0.88-2.12)	0.18
TVR	1.36 (0.88-2.12)	0.17
TLR	1.22 (0.72-2.06)	0.46
MACEs	1.29 (0.89-1.85)	0.17
Stroke	1.47 (0.44-4.89)	0.53

Bundhun P *et al. BMC Cardiovasc Disord.* 2017 Jul 17;17(1):190

FLOP: EXERCISE, EFFICACY & ETHICS

The importance of exercise

24 studies (n=936) of exercise at least 3 times a week for at least 5 weeks

73% male, majority on ART (19/24 studies)

Exercise *vs* no exercise significantly improved:

- Cardiorespiratory status
- Strength
- Body composition
- Depression symptoms
- Quality of life (SF-36 questionnaire)

No impact on CD4 or viral load (?!)

But… could there be HARM?!

O'Brien KK *et al. BMC Infect Dis.* 2016 Apr 26;16:182

Swiss cohort: physical activity (PA)

- **General population evidence:** PA associated with lower mortality, primarily due to fewer CV deaths
- 10,540 patients completed ≥1 PA self-report 12/2009 to 11/2014 during routine 6/12 clinical follow-up:
  - Year 1 unreliable as *higher rate of non-response*
  - **2010 to 2014:** no free-time PA at all declined from **49% to 44%** but % reporting sedentary work increased from **23% to 26%**
  - General population surveys in 2008 and 2014, showed fewer reporting no sports activities at all (**27%** in 2008; **26%** in 2014).
- ***"Integrating PA counselling into routine HIV care has potential to improve general health/QoL & reduce CVD"***

Schäfer J *et al. AIDS Care*. 2017 Aug;29(8):1056-1061

Study	Ethics	Results	Conclusion
Retrospective French cohort 2013-2015[1]	No; ART choice by local experts	N=21 on mDTG, no VF or RAMs	Safe & effective
Spanish study at EACS with I/E criteria[2], but retro cohort by paper[3]	None	1 VF, G118R in DNA at W24 + RNA by W36; switched W72[4]	These data suggest efficacy of mDTG as maintenance
Dutch prospective case series of n=5[5]	No	4 stayed suppressed; 1 VF without RAMs	Might be a valuable maintenance option
Katlama study[6] French observational study switch in suppressed	Not formal (all counselled & agreed)	N=28, 3 VF with INI RAMs by W 24 (nil on baseline DNA)	mDTG has potency for further investigations
Italian case series of NRTI refusers[9]	No	N=9, all stayed suppressed on mDTG	Larger studies warranted
DOLUMONO retro German cohort[7]	No	N=31 with 24W FU; 2 +VL, 1 with new RAMs	Caution is warranted
DOMONO Dutch RCT[8]: ART vs mDTG IS *vs* DS, zenith VL<100k.	Yes, trial registered	IS (n=51) vs DS (n=53) non-inf W24 (1 vs 0 VL >200); after DS 8% VF with therapeutic [DTG], 3/8 INI RAMs, STOPPED	mDTG non-inferior up to 24W but VF & RAMs thereafter, DTG should not be used as maintenance

1. Gubavu C *et al., J Antimicrob Chemother.* 2016 Apr;71(4):1046-50; 2. Rojas J *et al.,* EACS 2015; Abstract LBPS4/2; 3. Rojas J *et al., J Antimicrob Chemother.* 2016 Jul;71(7):1975-81; 4. Brenner BG *et al., J Antimicrob Chemother.* 2016 Jul;71(7):1948-53; 5. Rokx C *et al., J Antimicrob Chemother.* 2016 Jun;71(6):1632-6; 6. Katlama C *et al., J Antimicrob Chemother.* 2016 Sep;71(9):2646-50 7. Oldenbuettel C *et al., Antivir Ther.* 2017;22(2):169-172; 8. Wijting I *et al., Lancet HIV.* 2017 Dec;4(12):e547-e554; 9. Lanzafame M *et al., J Acquir Immune Defic Syndr.* 2016 May 1;72(1):e12-4

Editorial

INTERNATIONAL MEDICAL PRESS

Antiviral Therapy

Dolutegravir monotherapy: when should clinical practice be clinical research?

Joel Gallant, Jeremy Sugarman

Antiviral Therapy 2016; 10.3851/IMP3113

Submission date 31st October 2016
Acceptance date 2nd November 2016
Publication date 15th December 2016

Gallant J *et al. Antivir Ther.* 2017;22(2):93-95

Editorial

- Accompanied retrospective n=31 DTG mono cohort
- No consent/ethics beyond permission to analyse
- Based on “clinical judgement of treating physician”
- Reasons for switch listed:
  - Most would have had alternative switch options
  - Some were tenuous (anaemia, lipodystrophy)
- Since DTG mono not tested/recommended, how did they find 31 patients to switch?

Gallant J *et al. Antivir Ther.* 2017;22(2):93-95

Rationale unclear

- What motivated these decisions?
- How were individual potential benefits/risks balanced?
- Were discussed with colleagues with HIV expertise?
- How were patients engaged in deciding to be treated with an unproven & nonstandard single drug regimen?
- Were they made aware of the risks?
- Was there explicit informed consent for this clinical choice?
- **The answers to these important questions are not found in the paper**

REJECT

Gallant J *et al. Antivir Ther.* 2017;22(2):93-95

Key points

- This paper quotes 3 ‘studies’ with no ethics/consent
- Recruitment to all 4 **pre-date** DTG/3TC dual data
- “Retrospective” yet authors refer to “24W study period”
- Labs at W4/12/24 incl. GGT, CD8, CD4/CD8 ratio, lipids
- Unusual regimen – monitoring suggests study pre-planned
- Obtaining ethics **after** intervention simplifies ethics approval process but no protection of informed consent
- Clinical practice *vs* research confusing, a systematic evaluation of DTG mono is **clearly research**

WHY WAS IT ACCEPTED?

Gallant J *et al. Antivir Ther.* 2017;22(2):93-95

NEVER FINISH ON A LOW POINT…

https://www.cdc.gov/hiv/library/dcl/dcl/092717.html accessed 5th December 2017

Thank you!

?

lwaters@nhs.net
@drlaurajwaters