HIV treatment revision: As simple as old versus new?

David Nolan

Department of Immunology, Royal Perth Hospital, Western Australia

Institute for Immunology and Infectious Diseases, Murdoch University, Western Australia

Royal Perth Hospital

MURDOCH UNIVERSITY

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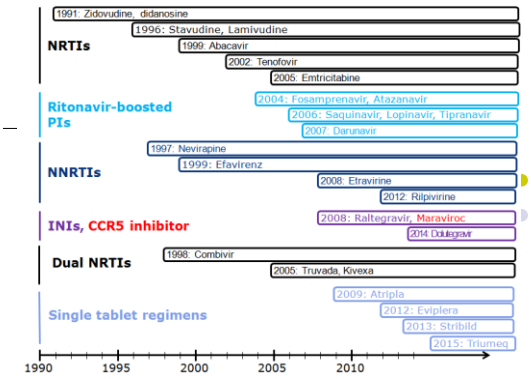
"Switching from old regimens"

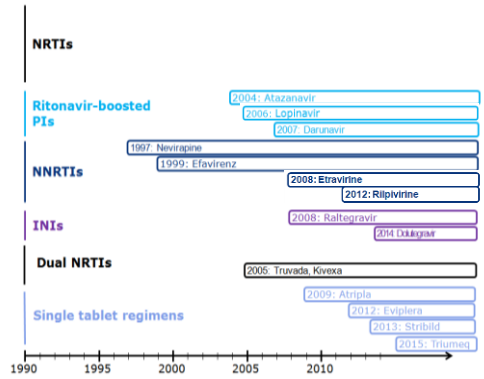
Pre-HAART era	'Early' HAART era	'Late' HAART era
HIV uncontrolled/poorly controlled, poor long-term prognosis	**HIV well controlled, long-term prognosis improved**	HIV well controlled, long-term prognosis improved
High-dose mono/dual NRTI therapy: limited treatment options	Multiple ART regimens: ↑choice but ?relative efficacy	**Multiple ART regimens: greater choice of equally highly effective HAART**
Issues of drug toxicity outweighed by need for survival benefit	Drug toxicity asumes more importance, but efficacy paramount	**Improved drug safety + tolerability, better understanding and monitoring of drug toxicity**
Advocacy focused on access to therapy	Advocacy focused on access + improved therapy tolerability + long-term outcomes	Advocacy focused on drug tolerability, long-term outcomes and specific management of complications

1987 1995 2000-2002 onwards

What is an "old regimen"?



What is an "old regimen"?



Switching for dosing simplification?

Pre-HAART era	'Early' HAART era	'Late' HAART era
		
High-level, multiple-doses per day regimens	**Twice**-daily co-formulated regimens	**Once**-daily co-formulated regimens
AZT (1987) **Initially 4-hourly, day + night**	**AZT + 3TC (1997)** **AZT + 3TC + ABC (2000)**	**ABC + 3TC (2004)** **TDF + FTC (2004)** **TDF + FTC + EFV = Atripla (2006)**

1987 1995 2000-2002 onwards

(developed world) (developed world)

Switching for dosing simplification?

Contemporary HAART: once-daily one-pill regimens

		
Baseline VL <10⁵ copies/mL Take with food Drug interaction: PPIs	Any viral load No food requirement Drug interaction: CYP3A4*	Any viral load (HLA-B*57 –ve) No food requirement Drug interaction: Metformin

TDF + FTC + Rilpivirine (Eviplera)

TDF + FTC + Elvitegravir + Cobicistat* (Stribild)

ABC + 3TC + Dolutegravir (Triumeq)

Switching for toxicity?

SQV (SAQUINAVIR) RIT (RITONAVIR) IDV (INDINAVIR) NFV (NELFINAVIR)	GI intolerance GI intolerance Nephrolithiasis, Skin ∆'s, ↑Bili Diarrhea	Dyslipidemia Hypertriglyceridemia Metabolic syndrome Metabolic syndrome
LPV (LOPINAVIR) ATZ (ATAZANAVIR) fosAPV (FOSAMPRENAVIR)	Diarrhea (capsule formulation) ↑Bilirubin, ECG changes (P-R) Skin rash, GI intolerance	↑Triglyceride, Metabolic syndrome
TPV (TIPRANAVIR) DRV (DARUNAVIR)	Rash, GI effects, Hepatotoxicity Rash	
PIs	Short-term toxicities	Long-term toxicities
AZT (1987): ZIDOVUDINE	GI effects, anemia, neutropenia	Lipoatrophy [~20%], anemia, LA
ddI (1991): DIDANOSINE		Neuropathy, pancreatitis, LA
ddC (1992): ZALCITABINE		Neuropathy+++
d4T (1994): STAVUDINE		Lipoatrophy [~50%], neuropathy, LA
3TC (1995): LAMIVUDINE		Alopecia (rare)
ABC (1999): ABACAVIR	Hypersensitivity [~5%]	
TDF* (2001): TENOFOVIR		Renal dysfunction [~5%]
FTC (2003): EMTRICITABINE	Skin hyperpigmentation	
NRTIs	Short-term toxicities (<3 months)	Long-term toxicities (3 to 36+ months)

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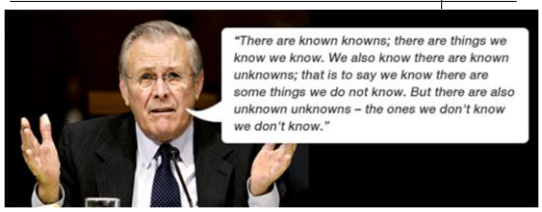
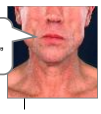
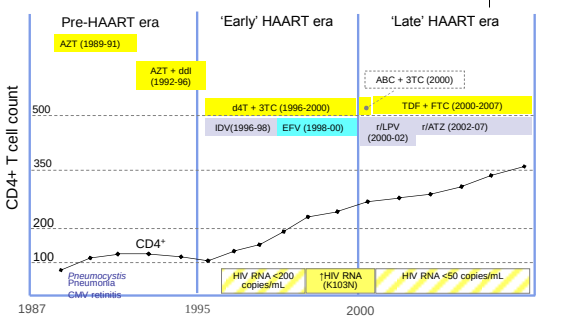


What do you do when you're asked to do nothing?





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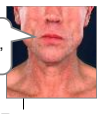
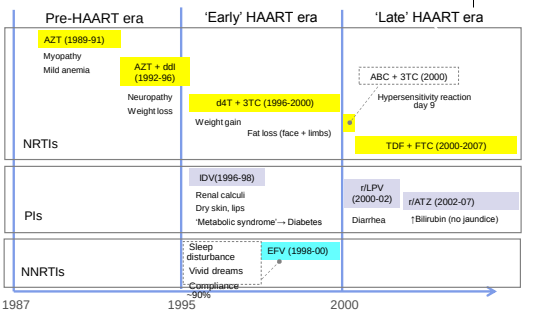
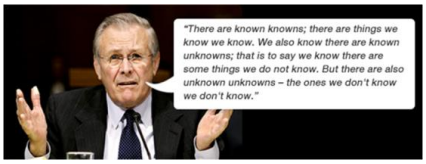






Applying the Rumsfeldian sieve

1. What do we know that we know?

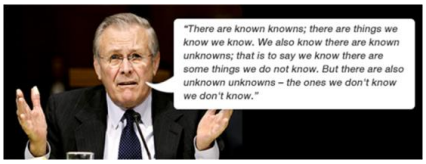
Plasma viral load <40 copies/mL on ART regimen X

CD4 T cell count 350 cells/μL (from nadir <100 cells/μL

Cardiovascular risk calculation: 12% 5-yr risk (63 yrs old)

Renal function and protein/creatinine ratio: eGFR >90, urine PCR 16 mg/mmol

FRAX score and BMD (+/- metabolic bone study): osteopenia



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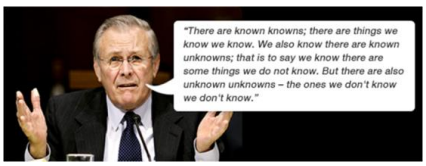


Applying the Rumsfeldian sieve

2. What do we know that we do not know?

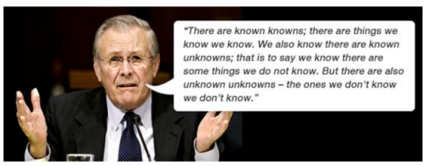
Plasma VL below 40 copies/mL, CSF or seminal fluid VL

Immune activation markers, esp innate (eg monocyte) markers

Cognitive function and risk of cognitive decline in future

Cancer risk?

Transmissibility risk?



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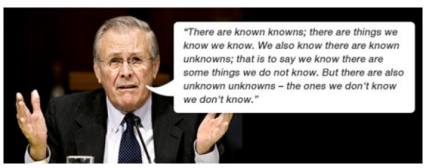
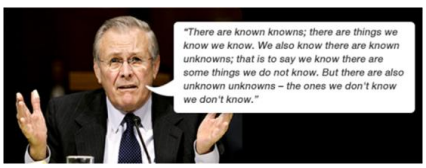


Applying the Rumsfeldian sieve

3. What don't we know that we do not know?

Do new drugs achieve better outcomes due to things that we can't measure?

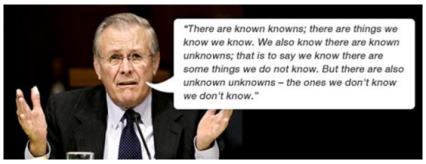
- Do they penetrate different sites?
  ... Brain (CPE), Monocytes (MES), genital tract?
- Do they do things beyond reduce viral load?
  ... Reduce innate immune activation?
- Do they have additional benefits?
  ... Reduce malignancy risk, or frailty ('inflammaging')



Applying the Rumsfeldian sieve

3. What don't we know that we do not know?

Does it matter that there are things we know we don't know?



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Treatment intensification, residual viremia and the latent reservoir… a long tale

A Randomized Open-Label Study of Three- versus Five-Drug Combination Antiretroviral Therapy in Newly HIV-1 Infected Individuals

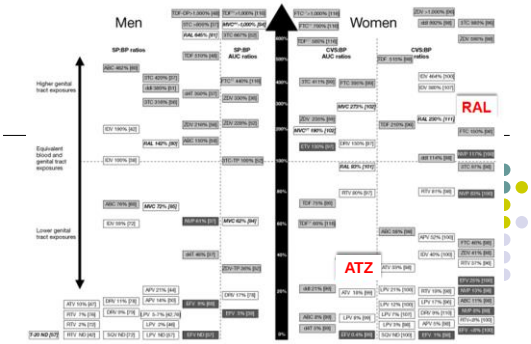
Martin Markowitz, M.D.[1], Teresa H. Evering, M.D., M.S.[1], Donald Garmon, N.P.[1], Marina Caskey, M.D.[2], Melissa La Mar, B.A.[1], Kristina Rodriguez, M.P.H.[1], Vincent Sahi, M.S.[1], Sarah Palmer, Ph.D.[3], Nicole Prada, Ph.D.[1], and Hiroshi Mohri, M.D. Ph. D.[1]

J Acquir Immune Defic Syndr. 2014 June 1; 66(2): 140–147.

Methods—40 newly HIV-1 infected patients were randomized 1:2 to receive 3-drug (N=14) or 5-drug (N=26) therapy. The primary endpoint was the percent of subjects with undetectable plasma viremia using standard RT-PCR and the single copy assay (SCA) after 48 weeks. Secondary endpoints included levels of cell-associated HIV-1 DNA and RNA and levels of infectious virus in resting CD4+ T cells at week 96 and quantitative and qualitative immunologic responses.

Results—At 48 weeks, 34 subjects remained on study and are included in the as-treated analysis. Three of 11 (27.3%) in the 3-drug arm and 9 of 21 (42.9%) in the 5-drug arm had plasma HIV-1 RNA levels below detection by both standard RT-PCR and SCA (P= 0.46, Fishers exact test). No significant differences in absolute levels of proviral DNA or changes in cell-associated RNA were seen during 96-weeks of therapy. Mean levels of infectious HIV-1 in resting CD4+ T cells at week 96 in 7 subjects treated with 3-drugs and 13 with 5-drugs were 0.67 and 0.71 IUPM respectively (P= 0.81). No differences were seen in quantitative or qualitative immunologic determinations including markers of immune activation.

Genital tract ART penetration



Else LJ, et al. Pharmacokinetics of antiretroviral drugs in anatomical sanctuary sites: the male and female genital tract. Antiviral Therapy 2011; 16:1149-1167

Genital tract ART penetration

Raltegravir Concentrations in the Genital Tract of HIV-1-Infected Women Treated with a Raltegravir-Containing Regimen (DIVA 01 Study)[9]

Cyril Clavel,[1]* Gilles Peytavin,[2] Roland Tubiana,[1] Cathia Soulié,[4] Catherine Crenn-Hebert,[3] Isabelle Heard,[2] François Bissuel,[6] Houria Ichou,[2] Claudia Ferreira,[5] Christine Katlama,[1] Anne-Geneviève Marcelin,[4] and Laurent Mandelbrot[1]

Antimicrobial Agents and Chemotherapy, June 2011, p. 3018–3021

BUT...

Study of TDF/FTC + Raltegravir (n=14) or Atazanavir (n=19) in HIV+ women

- Raltegravir CVL level 519% higher than Atazanavir (p<0.001)
- Genital tract VL <40 copies/mL in 90% of subjects, no difference by group
- No changes in cervical CD4+ or CD8+ cell activation markers by group

Meditz A, et al. Relationship between Genital Drug Concentrations and Cervical Cellular Immune Activation and Reconstitution in HIV-1 Infected Women on a Raltegravir versus a Boosted Atazanavir Regimen. AIDS Res Hum Retroviruses. 2015 May 21

Central nervous system penetration scores

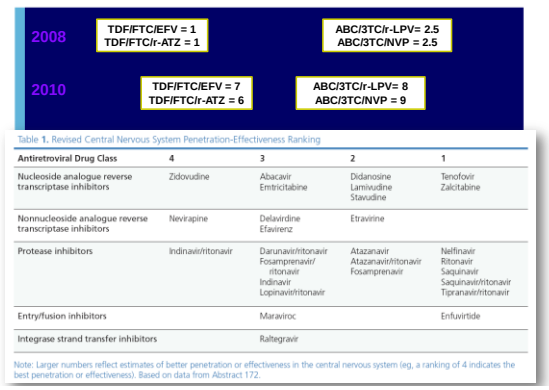


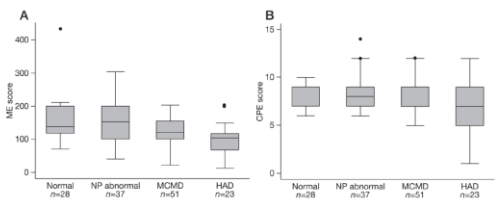
Table 1. Revised Central Nervous System Penetration-Effectiveness Ranking

Antiretroviral Drug Class	4	3	2	1
Nucleoside analogue reverse transcriptase inhibitors	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
Nonnucleoside analogue reverse transcriptase inhibitors	Nevirapine	Delavirdine Efavirenz	Etravirine	
Protease inhibitors	Indinavir/ritonavir	Darunavir/ritonavir Fosamprenavir/ritonavir Indinavir Lopinavir/ritonavir	Atazanavir Atazanavir/ritonavir Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir/ritonavir Tipranavir/ritonavir
Entry/fusion inhibitors		Maraviroc		Enfuvirtide
Integrase strand transfer inhibitors		Raltegravir		

Note: Larger numbers reflect estimates of better penetration or effectiveness in the central nervous system (eg, a ranking of 4 indicates the best penetration or effectiveness). Based on data from Abstract 172.

Antiretroviral monocyte efficacy score linked to cognitive impairment in HIV

Cecilia M Shikuma[1,*], Beau Nakamoto[1,2], Bruce Shiramizu[1], Chin-Yuan Liang[1], Victor DeGruttola[3], Kara Bennett[3], Robert Paul[4], Kalpana Kallianpur[1], Dominic Chow[1], Christina Gavegnano[5], Selwyn J Hurwitz[3], Raymond F Schinazi[5], and Victor G Valcour[6,7]



Antivir Ther. 2012 ; 17(7): 1233–1242.

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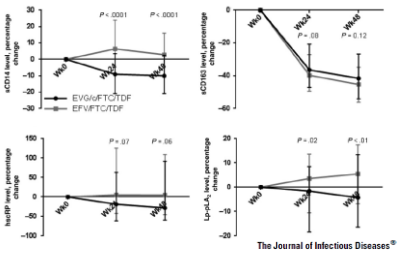
ARV drug	Acute infection in macrophages EC_{50}, nM	ME score[a]	CPE score (2010)
NRTI			
Abacavir sulfate	300	3 ⇩	3 ⇧
Didanosine	50	20	2
Emtricitabine[b]	80	12.5	3
Lamivudine	20	50	2
Stavudine	240	4	2
Tenofovir disoproxil fumarate	20	50	1
Zalcitabine	3	333	1
Zidovudine	20	50	4
NNRTI			
Delavirdine	10	100	3
Efavirenz	10	100	3
Nevirapine	50	20 ⇩	4 ⇧

Immune activation and integrase inhibitors

Differential Reduction in Monocyte Activation and Vascular Inflammation With Integrase Inhibitor–Based Initial Antiretroviral Therapy Among HIV-Infected Individuals

Carrilyn D. Hileman,[1,2] Bruce Kinley,[3] Valeska Schoen-Gaiel,[4] Kathy Melbourne,[4] Javier Szwarcberg,[4] Janet Robinson,[1] Michael M. Lederman,[1,2] and Grace A. Mccomsey[1,3]

100 Stribild Vs 100 Atripla



The Journal of Infectious Diseases® 2015;212:345–54

Cancer risk and ART

Exposure to Antiretroviral Therapy and Risk of Cancer in HIV-infected Persons

Chun CHAO[1], Wendy A. LEYDEN[2], Lanfang XU[1], Michael A. HORBERG[3], Daniel KLEIN[4], William J. TOWNER[5], Charles P. QUESENBERRY Jr.[2], Donald I. ABRAMS[6,7], and Michael J. SILVERBERG[2]

AIDS. 2012 November 13; 26(17): 2223–2231.

Adjusted rate ratio for cancer by duration of overall ART, PI and NNRTI use: adjusting for recent CD4 cell count and HIV RNA level.

	ADC	Infection-related NADC	Infection-unrelated NADC	Kaposi sarcoma	Non-Hodgkin lymphoma	Anal	Prostate	Lung	Hodgkin's Lymphoma
	Rate Ratio (95% confidence interval)								
Any ART use[1]									
Duration of use[2]	0.84 (0.78-0.90)	1.02 (0.92-1.13)	0.98 (0.92-1.03)	0.80 (0.72-0.90)	0.87 (0.78-0.96)	1.13 (0.99-1.30)	0.83 (0.74-0.94)	1.07 (0.93-1.24)	0.91 (0.73-1.14)
p for trend[2]	<0.01	0.67	0.41	<0.01	0.01	0.07	<0.01	0.33	0.41
PI use[3]									
Duration of use[2]	0.86 (0.80-0.94)	1.08 (0.98-1.18)	0.99 (0.94-1.04)	0.84 (0.75-0.94)	0.91 (0.82-1.00)	1.16 (1.02-1.31)	0.87 (0.77-0.98)	0.99 (0.86-1.13)	1.00 (0.81-1.22)
p for trend[2]	<0.01	0.11	0.66	<0.01	0.06	0.02	0.02	0.84	0.97
NNRTI use[3]									
Duration of use[2]	0.88 (0.78-1.00)	1.04 (0.92-1.18)	1.00 (0.93-1.07)	0.81 (0.67-0.99)	0.91 (0.77-1.06)	1.05 (0.89-1.23)	0.96 (0.83-1.11)	1.07 (0.90-1.27)	1.12 (0.87-1.43)
p for trend[2]	0.03	0.33	0.90	0.04	0.23	0.60	0.59	0.46	0.37

*Also noted in D:A:D study: J Acquir Immune Defic Syndr. 2015;68:568-77

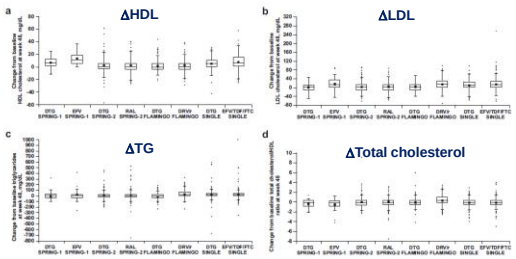
Lipids and integrase inhibitors vs EFV vs DRV

Comparative Changes of Lipid Levels in Treatment-Naive, HIV-1-Infected Adults Treated with Dolutegravir vs. Efavirenz, Raltegravir, and Ritonavir-Boosted Darunavir-Based Regimens Over 48 Weeks

Clin Drug Investig (2015) 35:211–219

Romina Quercia · Jeremy Roberts · Louise Martin-Carpenter · Carlos Zala

n=1,000 DTG pts over 4 studies



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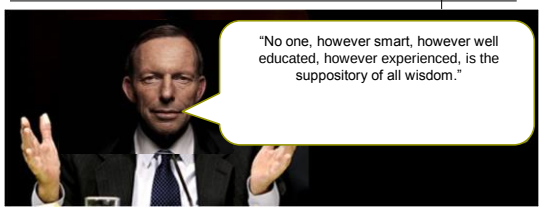

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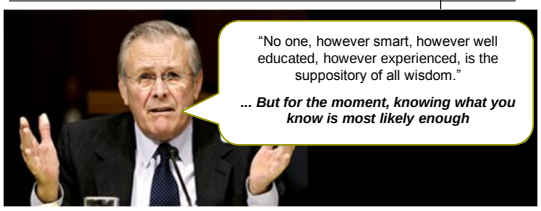

HIV treatment revision: Into the future?