NRTI toxicity

Francois Venter

Wits Reproductive Health & HIV Institute

Pipeline Report
http://www.pipelinereport.org

Welcome to the 2015 Pipeline Report

TAG i-base

Submitted by leichou on Tue, 07/10/2012 - 17:51

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July 17, 2015

HIV, HCV, and TB

Drugs, Diagnostics, Vaccines, Preventive Technologies, Research Toward a Cure, and Immune-Based and Gene Therapies in Development

Written by Polly Clayden, Simon Collins, Mike Frick, Mark Harrington, Tim Horn, Richard Jefferys, Erica Lessem, Lindsay McKenna, and Tracy Swan

Edited by Andrea Benzacar

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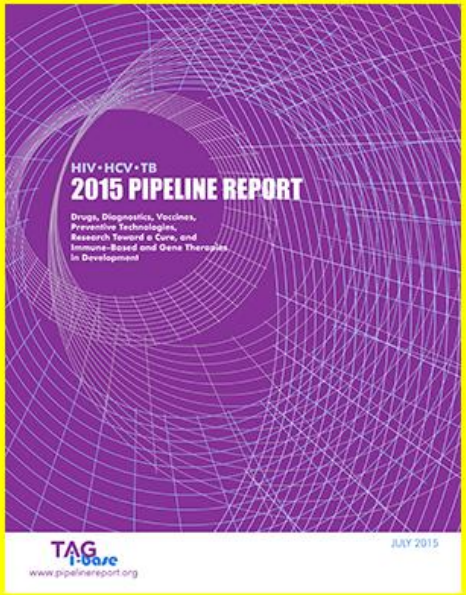

RHI

So what we got?

Current and Investigational Antiretrovirals

NRTIs/NtRTI

Abacavir
Didanosine
Emtricitabine
Lamivudine
Stavudine
Tenofovir
Tenofovir AF
Zidovudine

CYP3A4 In

Cobicistat

Thanks Howard Kessler

NNRTI

Doravirine
Efavirenz
Etravirine
Nevirapine
Rilpivirine

Fixed Combo

AZT/3TC
ABC/3TC
TDF/FTC
AZT/3TC/ABC
TDF/FTC/EFV
TDF/FTC/RPV
TDF/FTC/ETG/COB
ABC/3TC/DTG
TAF/FTC/ETG/COB

PI

Atazanavir
Darunavir
Fosamprenavir
Indinavir
Lopinavir/r
Nelfinavir
Ritonavir
Saquinavir
Tipranavir

Integrase In

Cabotegravir
Dolutegravir
Elvitegravir
Raltegravir

MI

Bevirimat
BMS-955176

EI/FI

Enfuvirtide
Maraviroc
BMS-663068

- 28 approved drugs, 5 classes
- Up to 10 recommended first-line regimens
- BUT: only 4 NRTIs that matter (if leave out 3TC/FTC)

An aside…


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Related information
Reyataz: EPAR
Kaletra: EPAR
Emtriva: EPAR

Nuke free/sparing initial ART

PI

- Atazanavir/r
- Darunavir/r
- Lopinavir/r

1 PI + 1 NNRTI	**NNRTI**: Efavirenz
1 PI + 1 INSTI	**INSTI**: Raltegravir
1 PI + 1 NRTI	**NRTI**: Lamivudine
1 PI + 1 FI	**FI**: Maraviroc

Nuke free/sparing initial ART

Study	Regimen	Comparison	Efficacy
SPARTAN	**ATV/r + RAL**	ATV/r + TDF-FTC	HIV-RNA <50 at wk 24: 74.6% vs 63.3% → **non-inferior** (but high bilirubinemia and resistance to RAL)
A4001078	**ATV/r + MVC**	ATV/r + TDF-FTC	HIV-RNA <50 at wk 48: 74.6% vs 83.6% → **non-inferior**
NEAT001/ ANRS143	**DRV/r + RAL**	DRV/r + TDF-FTC	Virological or clinical failure at wk 96: 17.8% vs 13.8% → **non-inferior** significantly inferior to standard therapy if CD4 <200/ml; trend for >100 000 c/mL
MODERN	**DRV/r + MVC**	DRV/r + TDF-FTC	HIV-RNA <50 at wk 48: 77.3% vs 86.8% → **inferior**
ACTG 5142	**LPV/r + EFV**	LPV/r + 2NRTI or EFV + 2NRTI	HIV-RNA<50 at wk 96: 83% vs 77% vs 89% → **non-inferior**
PROGRESS	**LPV/r + RAL**	LPV/r + TDF-FTC	HIV-RNA <40 at wk 96: 66.3% vs 68.6% → **non-inferior**
GARDEL	**LPV/r + 3TC**	LPV/r + 2 NRTI	HIV-RNA <50 at wk 48: 88.3% vs 83.7% → **non-inferior,** also >100 000 c/mL

Raffi et al., Lancet 2014; Riddler et al., NEJM 2008; Mills et al., JAIDS 2013;Kozal et al., HIV Clin Trials 2012; Reynes et a., AIDS Res Hum Retroviruses 2013; Cahn et al., Lancet Infect Dis 2014; Stellbrink, abstract AIDS 2014

Journal of Antimicrobial Chemotherapy Advance Access published January 7, 2016

J Antimicrob Chemother
doi:10.1093/jac/dkv429

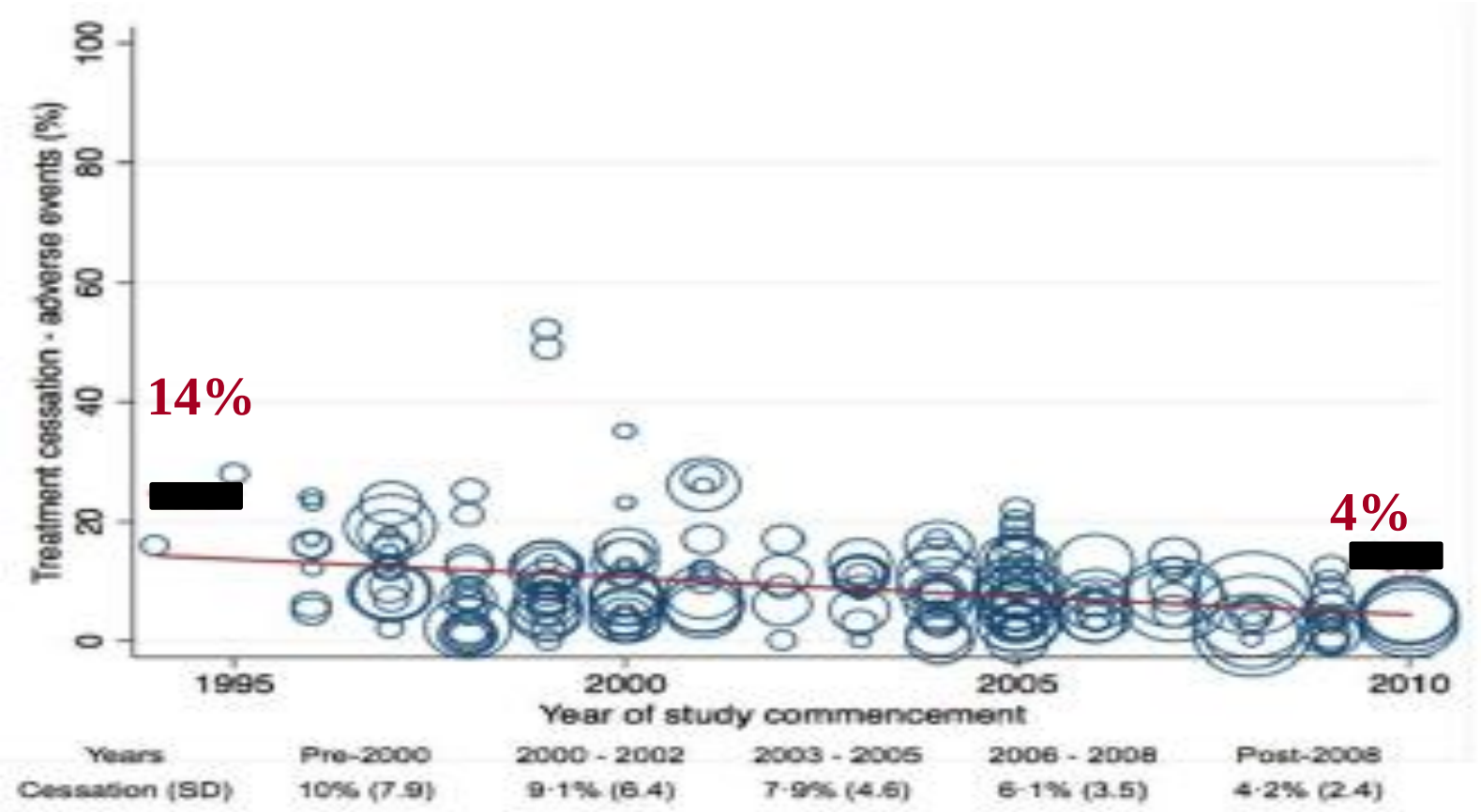
Journal of Antimicrobial Chemotherapy

Backbones versus core agents in initial ART regimens: one game, two players

Josep M. Llibre[1,2]*, Sharon Walmsley[3] and Josep M. Gatell[4]

ART Trials: Safety and Tolerability

114 studies, through 2012, up to 3 years of f/u: ITT analyses



Carr PLoS One 2014;9:e97482

Safety/Tolerability Rates

Study (reference)	Study arm (N)	Regimen	% d/c for adverse events at 96 wks
ECHO/THRIVE **Cohen AIDS 2013**	**682**	**2 NRTI + EFV**	**9%**
	686	**2 NRTI + RPV**	**4%**
SPRING-2 **Raffi Lancet Infect Dis 2013**	**411**	**2 NRTI + DTG**	**2%**
GS–US–236–0103: Rockstroh JAIDS 2013	**353**	**TDF/FTC/EVG/c**	**4%**
ACTG 5257 **Lennox Ann Intern Med 2014**	**605**	**2 NRTI + ATV/r**	**14%**
	601	**2 NRTI + DRV/r**	**5%**
	603	**2 NRTI + RAL**	**<1%**

Evolution of WHO ART Guidelines in Adults

Topic	2002	2003	2006	2010	2013
When to start	CD4 ≤200	CD4 ≤ 200	CD4 ≤ 200 - Consider 350 - CD4 ≤ 350 for TB	CD4 ≤ 350 -Irrespective CD4 for TB and HBV	**CD4 ≤ 500** -Irrespective CD4 for TB, HBV, PW and SDC - CD4 ≤ 350 as priority
1st Line	8 options - AZT preferred	4 options - AZT preferred	8 options - AZT or TDF preferred - d4T dose reduction	6 options &FDCs - AZT or TDF preferred - d4T phase out	2 options & FDCs - TDF and EFV preferred across all populations
2nd Line	Boosted and non-boosted PIs	Boosted PIs -IDV/r LPV/r, SQV/r	Boosted PI - ATV/r, DRV/r, FPV/r LPV/r, SQV/r	Boosted PI - Heat stable FDC: ATV/r, LPV/r	Boosted PI - Heat stable FDC: ATV/r, LPV/r
3rd Line	None	None	None	DRV/r, RAL, ETV	DRV/r, RAL, ETV
Viral Load Testing	No	No (Desirable)	Yes (Tertiary centers)	Yes (Phase in approach)	Yes (preferred for monitoring, use of PoC, DBS)

Earlier initiation

Simpler treatment

Less toxic, more robust regimens

Better monitoring

Not talking about…

- Pregnancy
- Paeds specifically – mitochondrial toxicity tends to be delayed

Lamivudine, emtricitabine

- 3TC – red cell aplasia (very rare) – presents as catastrophic anaemia, reversible (pancreatitis spurious)
- FTC – pigmentation on hands

- Zalcitabine (ddC)
- Didanosine (ddI)
- Stavudine (d4T)
- Zidovudine (AZT)
- Abacavir (ABC)
- Tenofovir (TDF)
- Tenofovir alafanamide (TAF)

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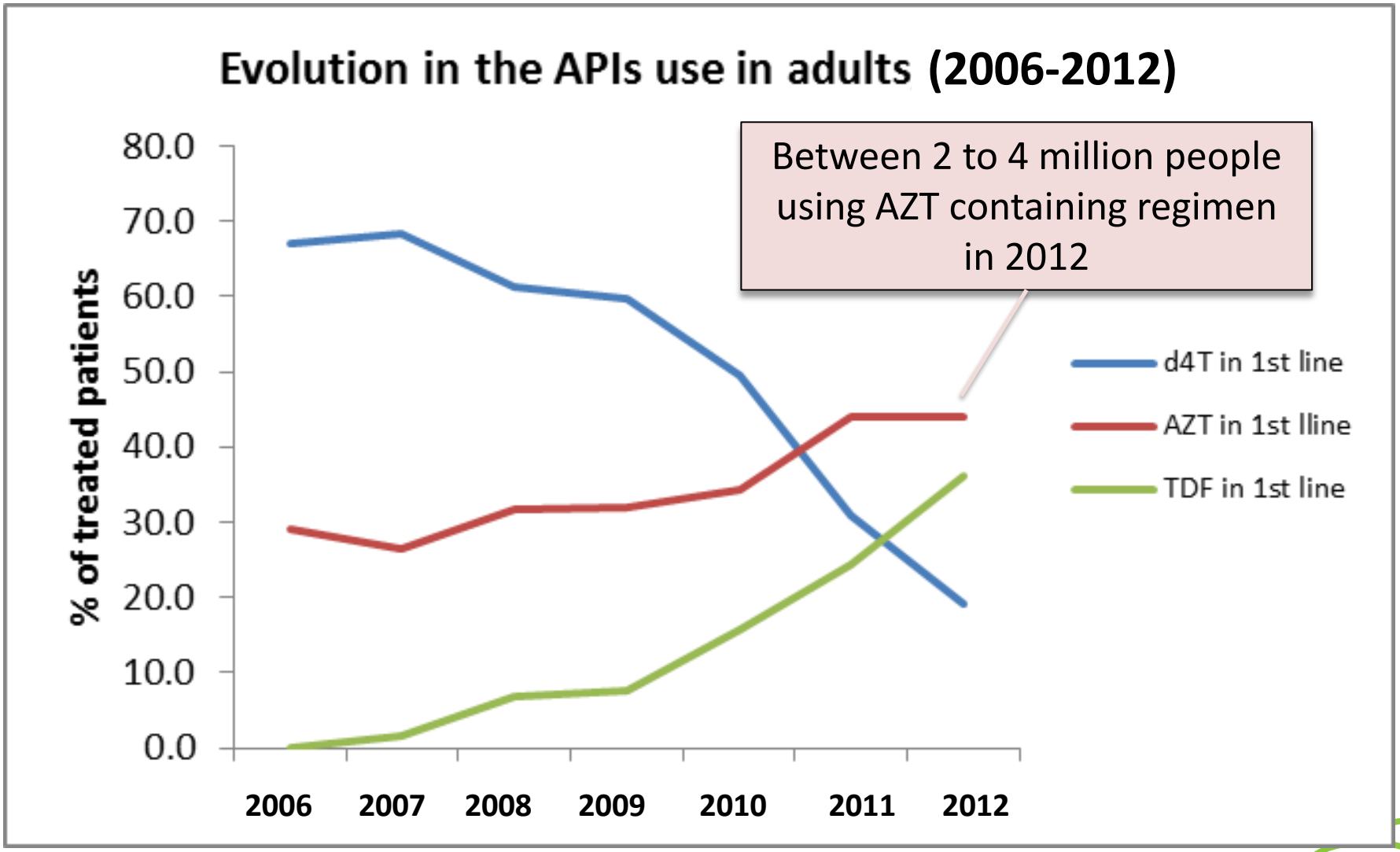
Changes in D4T, AZT & TDF use

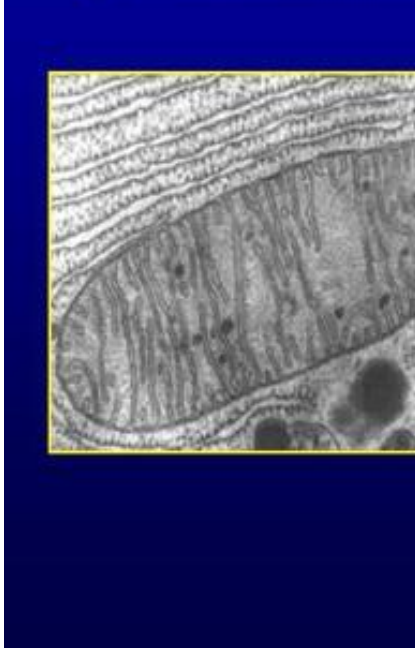


WHO AMDS database, 2014
(preliminary data)

Stavudine

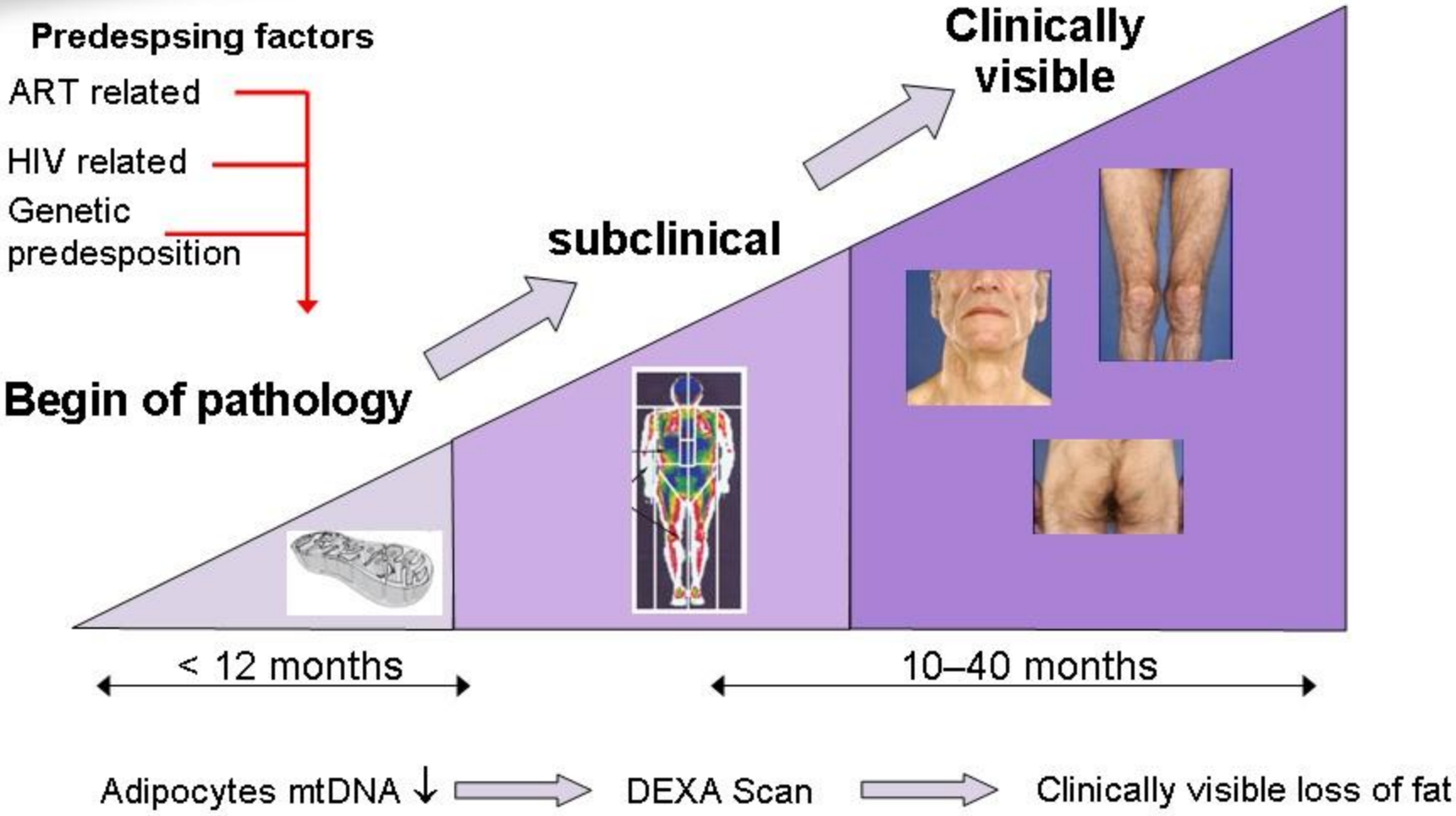
- VERY well tolerated in short term (<6 months with 30mg BD)
- Significant toxicity
- Lower dose being studied, but cost so close to TDF, not going to be a competitor
- Role in unstable patients

Toxicity



- Raised MCV
- Mitochondrial (?higher risk in women, high BMI)
  - Lipoatrophy
    - Often permanent
  - Peripheral neuropathy
  - Fatty liver
  - Lactic acidosis
    - Often fatal
  - ?pancreatitis

Pathogenesis of lipoattrophy begins before clinical signs are seen



Nolan D, *et al. Antivir Ther* 2003; **8**:617–626

- Steve Innes study: Low dose d4T in kids

- Zalcitabine (ddC)
- Didanosine (ddI)
- Stavudine (d4T)
- Zidovudine (AZT)
- Abacavir (ABC)
- Tenofovir (TDF)
- Tenofovir alafanamide (TAF)

AZT

- Toxic, dose reduction not successful
- ???any role for AZT in future???
- EARNEST – does it matter what the nukes are? Could we recycle TDF/FTC?

AZT toxicity

- Raised MCV
- GIT ++ (+++ if PEP!)
- Headache, malaise
- Mitochondrial toxicity – similar to d4T
- Anaemia – worse with more advanced disease, reversible
- Neutropaenia

- Zalcitabine (ddC)
- Didanosine (ddI)
- Stavudine (d4T)
- Zidovudine (AZT)
- Abacavir (ABC)
- Tenofovir (TDF)
- Tenofovir alafanamide (TAF)

ABC

- Preferred (with TDF) in some guidelines
- High levels of use in some countries
- Co-formulated with DTG

What's wrong with ABC?

- Good, safe drug
- Useful in renal failure
- Expensive (and dose reduction probably not an option)
- Some concerns re high VL
- Hypersensitivity - HLA testing required in caucasians
- ?link to cardiovascular disease
  - Risk decreases soon after cessation
  - Multiplicative with other risk factors

Sabin *et al. BMC Medicine* (2016) 14:61
DOI 10.1186/s12916-016-0588-4

BMC Medicine

RESEARCH ARTICLE Open Access

Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with HIV? A cohort collaboration

Caroline A. Sabin[1*], Peter Reiss[2], Lene Ryom[3], Andrew N. Phillips[1], Rainer Weber[4], Matthew Law[5], Eric Fontas[6], Amanda Mocroft[1], Stephane de Wit[7], Colette Smith[1], Francois Dabis[8], Antonella d'Arminio Monforte[9], Wafaa El-Sadr[10], and Jens D. Lundgren[3] for the D:A:D Study Group

Conclusions: Despite a reduction in the channelling of ABC for patients at higher CVD risk since 2008, we continue to observe an association between ABC use and MI risk. Whilst confounding cannot be fully ruled out, this further diminishes channelling bias as an explanation for our findings.

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Confirmed in other cohorts but NOT the company studies

Major Cohort Studies Evaluating an Association Between Abacavir Use and Cardiovascular Disease Risk

Study [ref] (N)	Design	Cardiovascular Events	Association Detected With Abacavir?
D:A:D [Worm 2010] (33,347)	Observational	Prospective, predefined	Yes*†
FHDH [Lang 2010] (1173)	Case-control	Prospective, MI retrospectively validated	No
SMART [SMART/D:A:D 2008] (2752)	Observational analysis of RCT	Prospective, predefined	Yes*†
STEAL [Martin 2009] (357)	RCT	Prospective	Yes‡
GSK [Cutrell 2008] (14,174)	54 RCTs	Retrospective, database search	No‡
ALLRT ACTG 5001 [Ribaudo 2011] (5056)	6 RCTs	Retrospective by 2 independent reviewers	No*
Veterans Admin [Bedimo 2011] (19,424)	Observational	Retrospective database search	No*†
HOPS [Lichtenstein 2010] (2005)	Observational	Prospective, predefined	No
Veterans Health Admin [Choi 2011] (10,931)	Observational	Retrospective, using VA database discharge and procedure codes	Yes†
Quebec (RAMQ) [Durand 2011] (7053)	Case-control	Retrospective, database search	Yes
FDA Meta-analysis[Ding 2011] (9874)	26 RCTs	Retrospective, database search	No
Triant et al.[Triant 2010] (6517)	Observational	Retrospective, database search	Yes†

RCT, randomized controlled trial.
**These individuals were more likely to receive abacavir; Majority of patients starting abacavir were treatment-experienced.*
†Patients with chronic kidney disease included.
‡Patients with chronic kidney disease excluded.

Most of the patients starting abacavir were reatment naive.

- Zalcitabine (ddC)
- Didanosine (ddI)
- Stavudine (d4T)
- Zidovudine (AZT)
- Abacavir (ABC)
- Tenofovir (TDF)
- Tenofovir alafanamide (TAF)

Tenofovir has taken over the world!

- 1st line recommendation by WHO; feature in EVERY guideline (some have ABC)
- Well tolerated, FDCs galore, daily
- Cheap (only alternative that is cheaper is d4T)
- Hep B for free

Infect Dis Ther. 2015 Jun; 4(2): 145–157.
Published online 2015 Jun 2. doi: 10.1007/s40121-015-0070-1
PMCID: PMC4471058

Tenofovir: What We Have Learnt After 7.5 Million Person-Years of Use

Andrew Ustianowski and Joop E. Arends

Author information ► Article notes ► Copyright and License information ►

Abstract

Go to:

Now add PrEP TDF…

Is API production capacity a potential treatment bottleneck?

Situation of API production capacity for TDF and EFV with major API producers (WHO API manufacturer survey, May 2013)

Major parameters	TDF	EFV
Number of API producers in 2012	7	8
API production capacity in 2012 (in metric tons)*	>1,500	>2,210
Estimated number of patients using regimens containing the API in end of 2012	3,500,000	3,700,000
Number of patients that could be treated in end of 2012	>13,800,000	>10,000,000

(*) Data from some major manufacturers were not reported.

The manufacturers also mentioned that they are all in the process of increasing capacity.

WHO HIV/AMDS, 2014 (preliminary data)

Is API production capacity a potential

Concern: API may become a huge problem if '20 by 20' AND PrEP come into play…

Situation API pr		
Major		
Number of 2012		
API produc 2012 (in m		
Estimated patients us containing 2012		
Number of patients that could be treated in end of 2012	>13,800,000	>10,000,000

ufacturers
tioned that
ll in the
f increasing

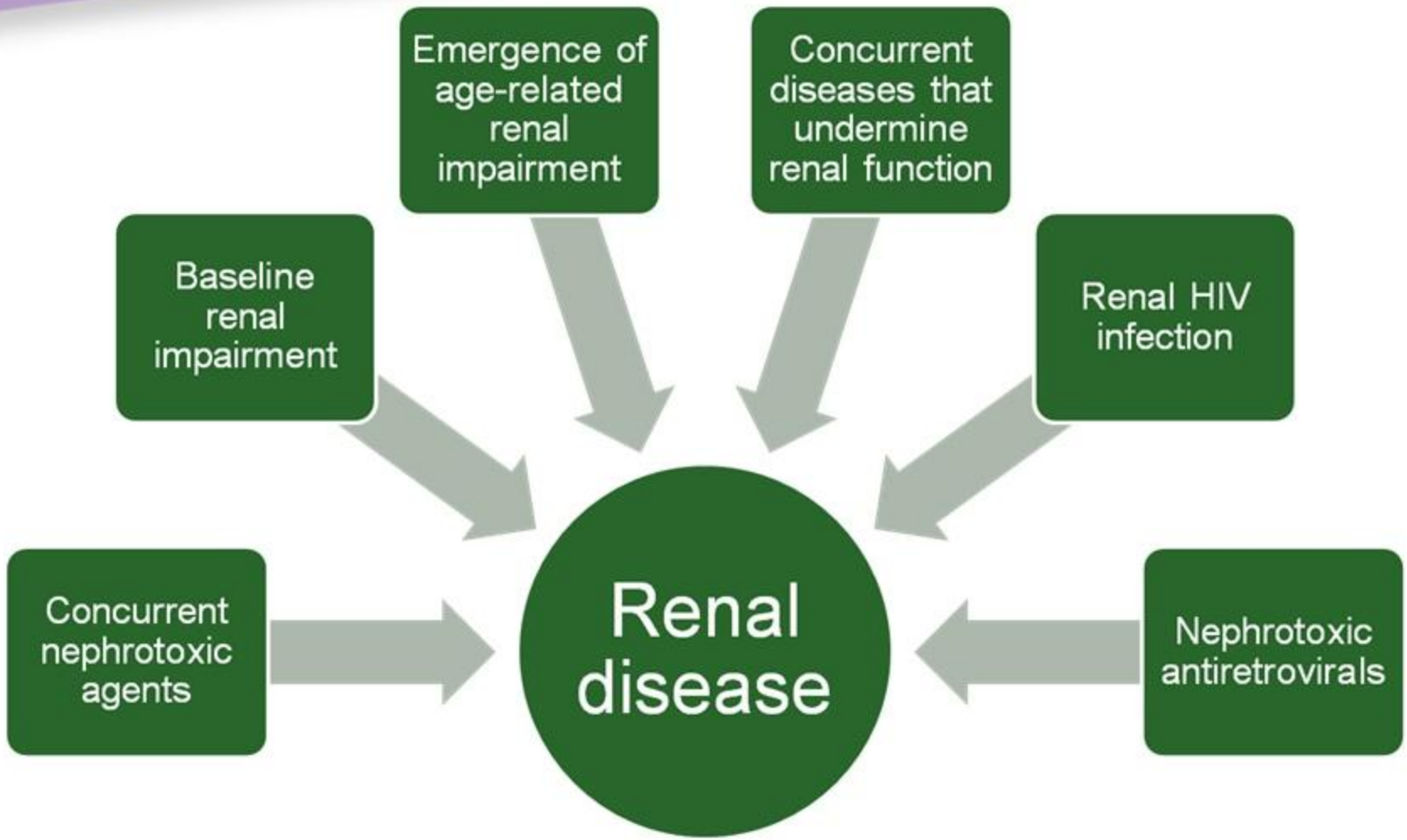
(*) Data from some major manufacturers were not reported.

WHO HIV/AMDS, 2014
(preliminary data)

Tenofovir toxicity

- VERY safe
- Mild GIT effects - nausea

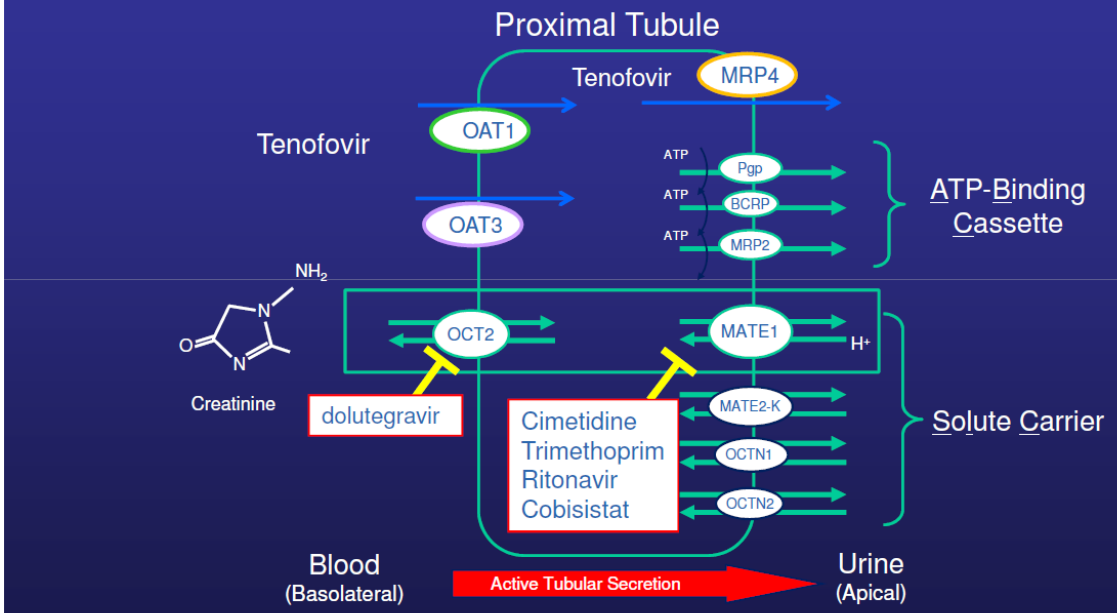
Long-term toxicity: renal disease



Kidneys and TDF

- Unusual
- Tubular problems AND decreased GFR (?clinical significance) – GFR dip, then stabilises (also seen in PrEP)
- But very safe – even if renal dysfunction (Lloyd Mulenga, CID)
- Worse with boosting (esp Fanconi's)
- Dipstix inadequate for monitoring
- Renal toxicity USUALLY reversible
- PrEP: 40 000 patients (but screened)

Is Creatinine and eGFR the right model for CKD when on HAART?



MATE: multidrug and toxic compound extrusion

Cihlar T, et al. Antivir Ther. 2007;12:267–72. Tong L, et al. Antimicrob Agents Chemo. 2007;51:3498–504.n Meyer HE, et al. Am J Physiol Renal Physiol. 2010; 298:F997–F1005.

Bone and TDF

- Data consistent – DEXA, observational studies, PrEP
- Clinical outcomes still speculative – but worrying
- Seems like impact is in first year
- Somewhat reversible
- Low dose d4T study will help us (DEXA and tubular function)

- Zalcitabine (ddC)
- Didanosine (ddI)
- Stavudine (d4T)
- Zidovudine (AZT)
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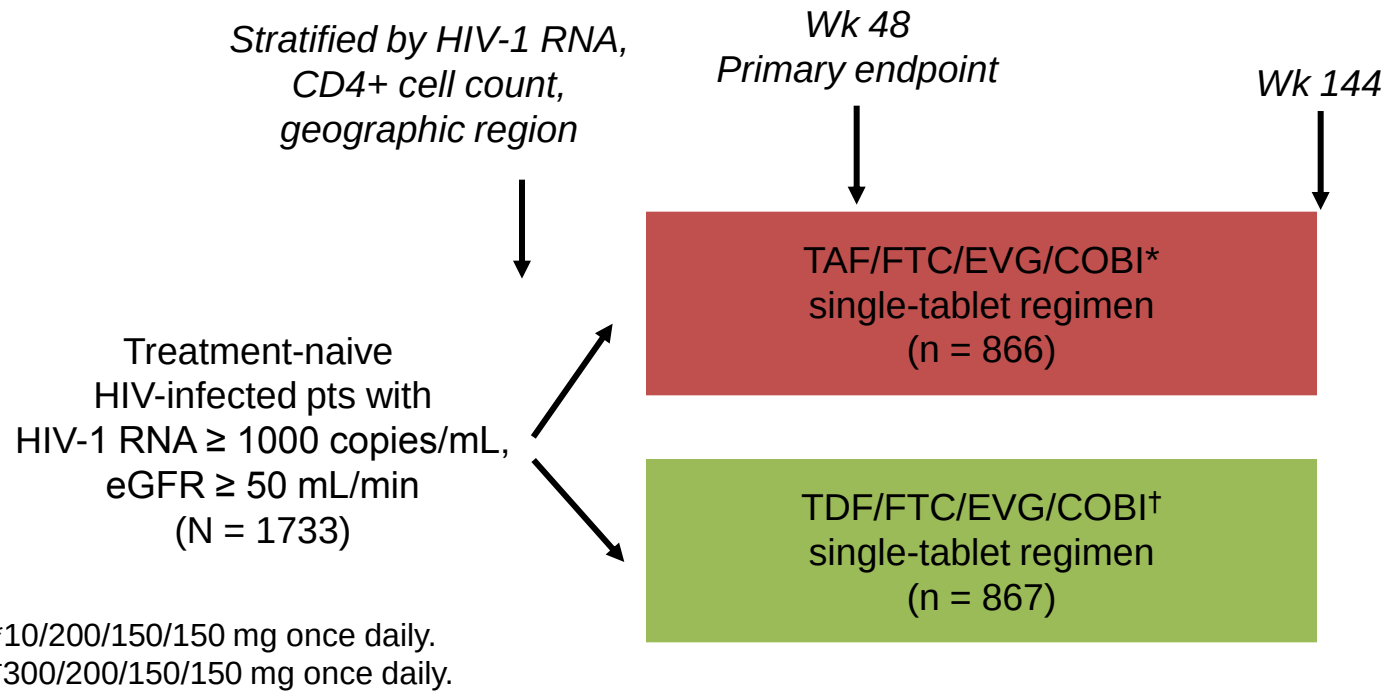
- Tenofovir alafanamide (TAF)

Tenofovir alafenamide

- Slightly better safety profile than TDF (at 10 or 25mg vs 300mg).
- But being tested as co-formulations
- Co-formulations – estimated availability to LMIC 2019

Studies 104/111: Tenofovir Alafenamide Fumarate vs TDF in Treatment-Naive Pts

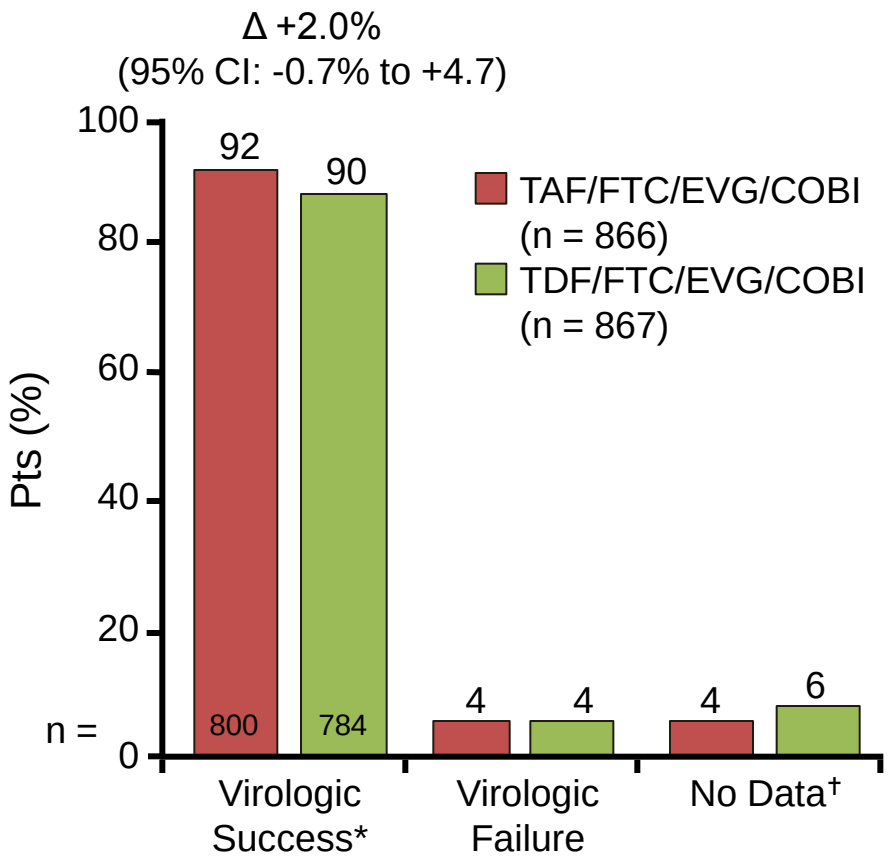
- Parallel, randomized, double-blind, active-controlled phase III studies
- Primary endpoint: HIV-1 RNA at Wk 48



*10/200/150/150 mg once daily.
†300/200/150/150 mg once daily.

Wohl DA, et al. CROI 2015. Abstract 113LB.

Studies 104/111: TAF Noninferior to TDF at Week 48

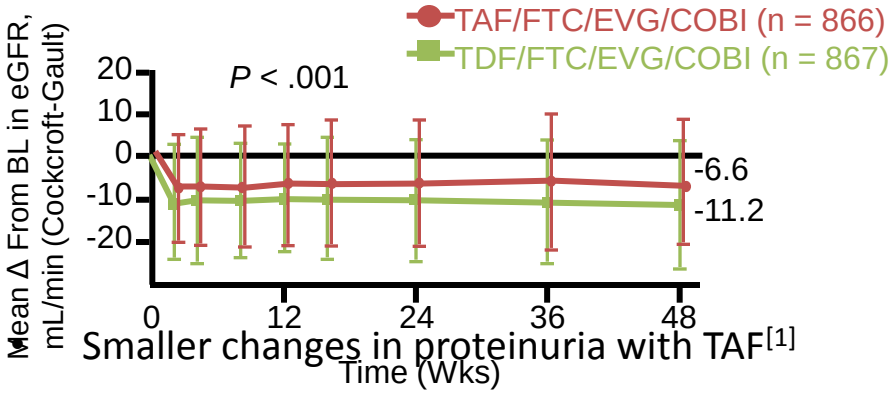


- TAF also noninferior to TDF at Wk 48 in each study (104 and 111)
- Results similar across all baseline virologic and demographic subgroups
- 7 pts in TAF arm and 5 pts in TDF arm with NRTI resistance at VF
  - 1 in TAF arm and 2 in TDF arm with combined M184V/I + K65R
- 5 pts in TAF arm and 3 pts in TDF arm with INSTI resistance at VF
- 0.9% in TAF arm and 1.5% in TDF arm discontinued due to AE
- CD4+ increases greater in TAF arm: 211 vs 181 (*P* = .024)

Wohl DA, et al. CROI 2015. Abstract 113LB. Reproduced with permission.

Renal Markers With TAF and TDF at Wk 48

- Smaller decreases in eGFR with TAF[1]



- Smaller changes in proteinuria with TAF[1]

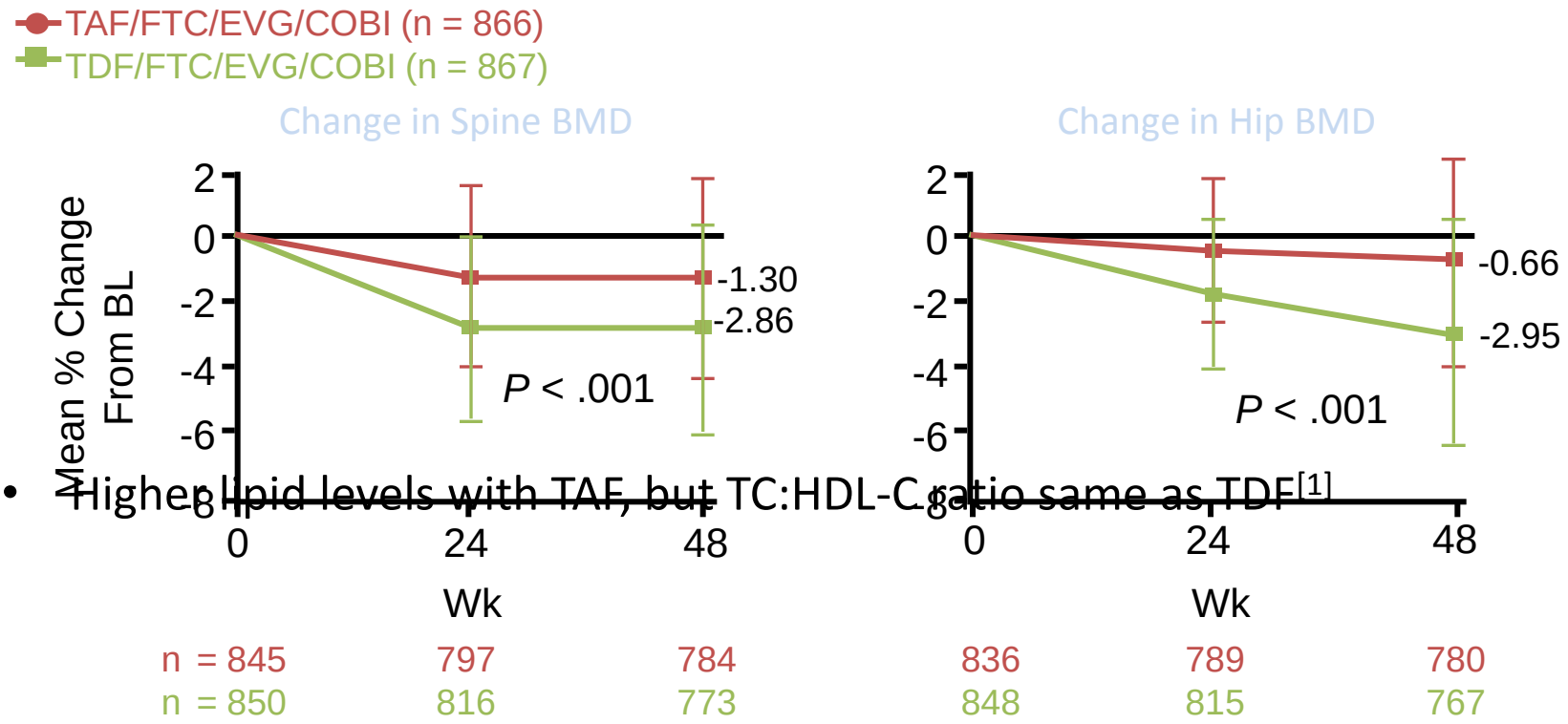
Median % Change From BL in Urine Protein:Creatinine Ratio			
Marker	**TAF (n = 866)**	**TDF (n = 867)**	***P* Value**
Albumin	-5	+7	< .001
β_2-microglobulin	-32	+24	< .001

- In separate single-arm trial of virologically suppressed pts with eGFR 30-69 mL/min switched to open-label TAF/FTC/EVG/COBI[2]
  - 65% on TDF at BL
- At Wk 48 after switch:
  - 92% maintained virologic suppression
  - No change in eGFR
  - Reduction in proteinuria and markers of renal tubular function
  - Improvement in hip and spine BMD

1. Sax P, et al. CROI 2015. Abstract 143. Reproduced with permission. 2. Pozniak A, et al. CROI 2015. Abstract 795.

Studies 104/111: Significantly Smaller Decline in Hip and Spine BMD With TAF

- Significantly smaller decline in hip and spine BMD with TAF



- ~~Higher lipid levels with TAF, but~~ TC:HDL-C ratio same as TDF[1]

Sax P, et al. CROI 2015. Abstract 143. Reproduced with permission.

Where to NRTIs?

- d4T study will part-answer TDF bone and renal worries; otherwise, just wait
- TAF likely to replace it
- DTG/3TC may be disruptive
- Lower doses d4T; ABC, other drugs unlikely to displace it