BHIVA guidelines on the treatment of HIV-1-positive adults with antiretroviral therapy

START & other changes

Contents

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The 2015 guidelines

- Consultation completed 17th July 2015
- Community consultation and the final guidelines panel meeting held on 6th August 2015
- Peer review by three European experts
- Published online end September 2015
- Since 2012
  - Guidelines development has followed the GRADE process
  - NICE accredited

Guideline limitations

- Trial populations are not real life populations
- Study designs are heterogeneous
- Trials may not be performed in important scenarios
- An alternative strategy may be better than a preferred strategy
- Experts may be prone to bias

Treatment aims

- The primary aim of ART is the prevention of the mortality and morbidity associated with chronic HIV infection at low cost of drug toxicity
- Treatment should improve the physical and psychological wellbeing of people living with HIV

Resource use

- In developing the recommendations, differences in critical treatment outcomes were taken into account to determine preferred and alternative regimens
- Commissioning arrangements and local drug costs will and should influence ART choice where outcomes, across a range of clinical measures, are similar between individual drugs
- Lower costs should not compromise efficacy or quality not least because poorer outcomes will have a longer-term cost impact

When to start

When to start 2012

- **We recommend starting ART in patients:**
  - With chronic HIV and CD4 cell count ≤350 cells/mm^3 (1A)
  - To prevent transmission
  - With the following conditions:
    - AIDS [1A], HIV-related co-morbidity (1C), HBV (1B) and HCV (1C) if the CD4 count is ≤500 cells/mm^3,non-AIDS-defining malignancies requiring immunosuppressive radiotherapy or chemotherapy (1C)

- **We suggest starting ART in patients:**
  - With HBV and CD4 cell count >500 cells/mm^3 + HBV treatment indicated (2B)
  - Expanded to include HCV in the 2013 interim update

High CVD risk was a reason for earlier ART in 2008 guidelines but removed from 2012 update

http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf

When to start 2015

- We recommend people with HIV start ART (1A)
- The situations where ART was recommended at higher CD4 cell counts in the 2012/3 guidelines retain relatively 'urgent' status
  - Primary HIV
  - HIV-related conditions, e.g. HIVAN, malignancies
  - HCV/HBV co-infection
  - Prevention of transmission

http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf

Rationale for change to 'when to start'

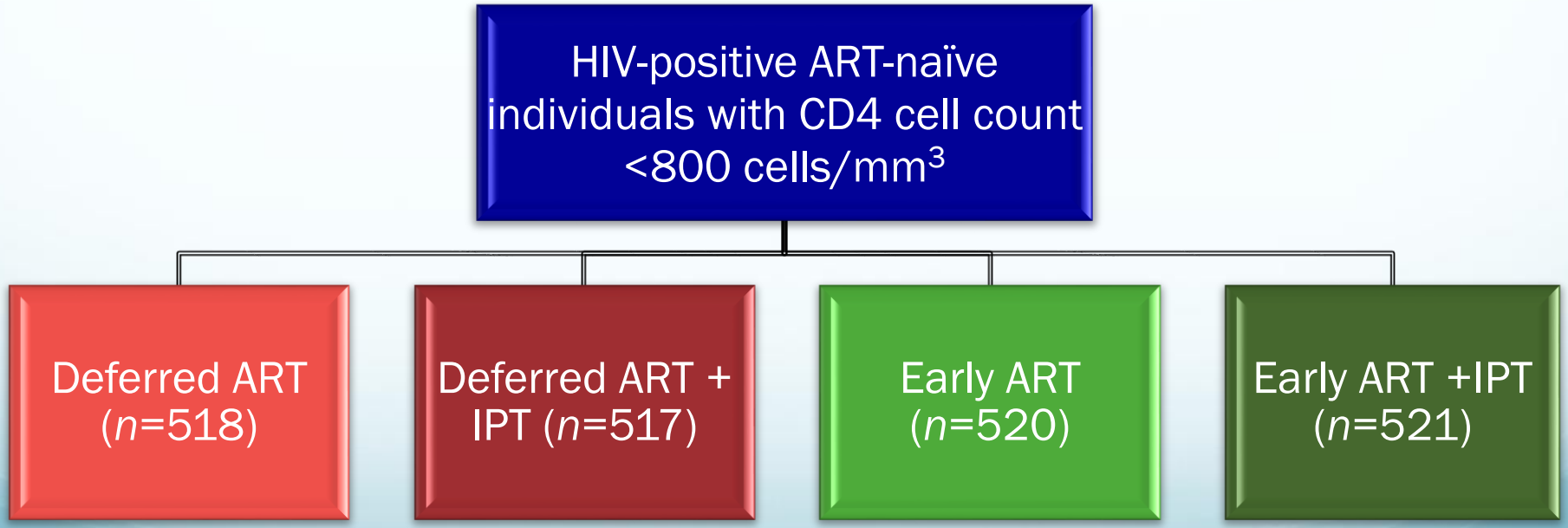
- When 2012/3 guidelines were developed, the data supporting early ART came largely from cohorts and were conflicting:
  - NA-ACCORD
    - US analysis
    - Significantly lower mortality if ART at CD4 >500 cells/mm^3 vs defer
  - ART-CC
    - European analysis
    - No clear benefit of ART at CD4 >375 cells/mm^3 with respect to AIDS/mortality
- *Post hoc* analysis of SMART suggested earlier ART beneficial

Rationale for change to ‘when to start’

- The change to the 2015 guidelines was based on results of **randomised controlled trials**:
  - TEMPRANO
  - SMART

TEMPRANO

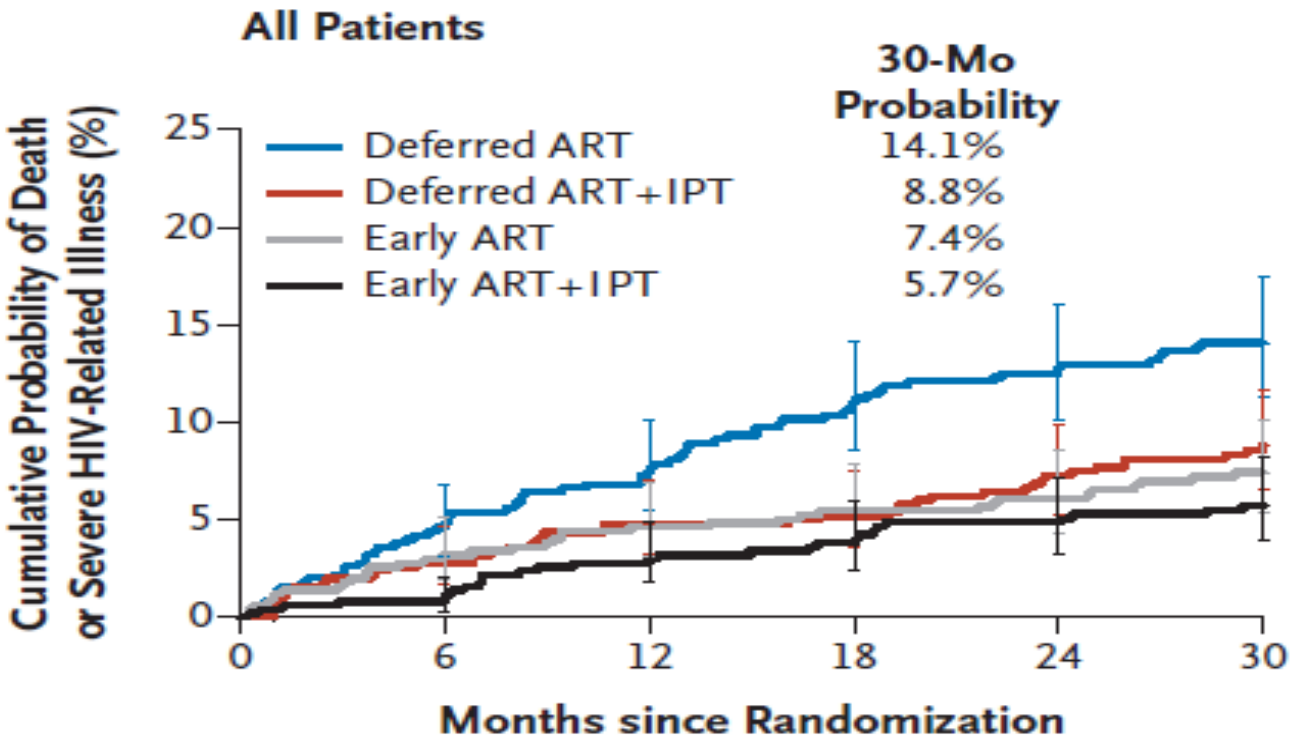
- Ivory Coast RCT Septrin if CD4 <500 cells/mm^3
- The primary composite endpoint = AIDS event, non-AIDS cancer, non-AIDS bacterial invasive disease or death from any cause. Main secondary endpoint = any G3/4 event



The TEMPRANO ANRS 12136 Study Group. NEJM 2015; 373: 808-822.

TEMPRANO

A Primary Outcome



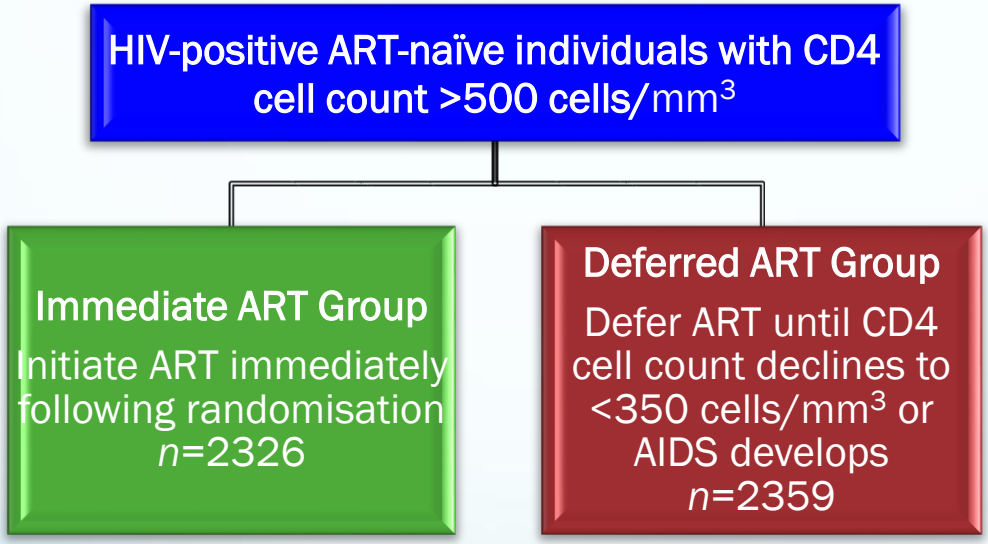
No. at Risk

Deferred ART	511	473	448	418	400	366
Deferred ART+IPT	512	489	473	459	440	419
Early ART	515	481	463	452	432	403
Early ART+IPT	518	501	478	459	445	418

The TEMPRANO ANRS 12136 Study Group. NEJM 2015; 373: 808-822.

START

- International RCT of immediate vs deferred ART
- The primary composite endpoint = a serious AIDS event, serious non-AIDS event, or death from any cause



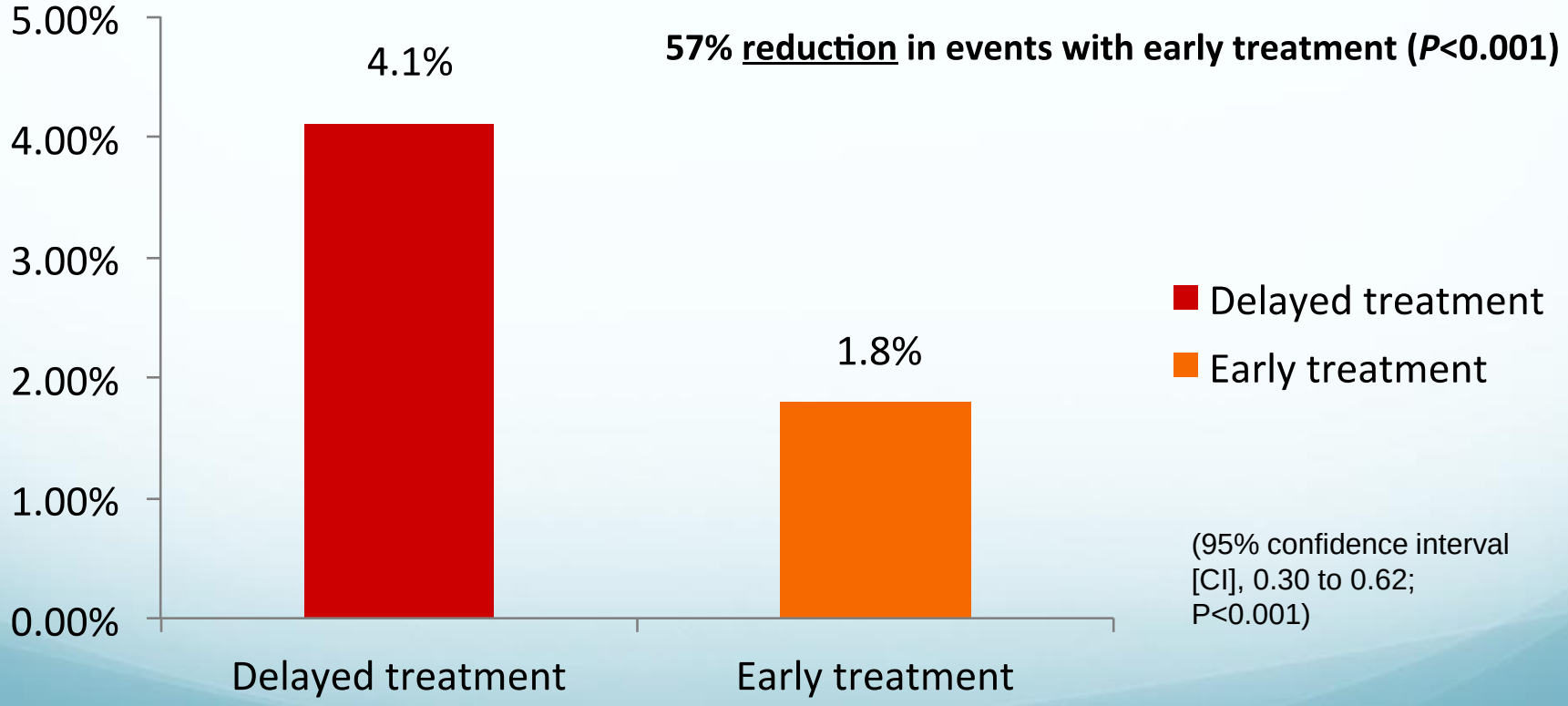
Characteristic	*N*=4685
Age (year)*	36 (29–44)
Female, *n* (%)	1257 (27)
Race, *n* (%)	
White	2086 (45)
Black	1410 (30)
Time since HIV diagnosis (year)*	1.0 (0.4, 3.1)
CD4 cell count (cells/mm^3)*	651 (584–765)
Baseline HIV-RNA (copies/mL)*	12,759 (3019–43,391)
TDF usage	89% in both groups

* Median (IQR)

- On 15 May 2015, at a planned interim review, DSMB recommended participants in the deferred arm not already on ART should be offered ART and follow-up should continue with all subjects on therapy. LFU (last contact >10/12) 4% immediate & 5% deferred

START: primary results

Hazard of developing AIDS, serious non-AIDS events or death



1. Lundgren D, et al. IAS 2015. Vancouver, CAN. Oral # MOSY03;
2. Lundgren D, et al. NEJM 2015 Published Epub ahead of print July 20, 2015 DOI: 10.1056/NEJMoa1506816

Primary results

after mean FU 3 years when 98% immediate and 48% deferred arm on ART

Primary endpoint (Final analysis)	Immediate ART	Deferred ART	Hazard ratio
AIDS, serious non-AIDS, or death *PY = patient years	42 events (1.8%) 0.60/100PY	96 events (4.1%) 1.38/100PY*	0.43 (0.30–0.62) *P*<0.001

Starting HIV therapy at CD4 count >500 cells/mm^3 compared to deferring start until CD4 was <350 cells/mm^3 resulted in:

- **57% reduced risk of the primary composite outcome of AIDS events, serious non-AIDS events, or death in the immediate arm versus the deferred arm**

Combination antiretroviral therapy (ART) should be recommended for all HIV-positive persons regardless of CD4 cell count

START: results

Results:

	Immediate No of Events (%)	Deferred No of Events (%)	HR Imm/Def	Risk reduction	P value
Primary Endpoint	42 (1.8%)	96 (4.1%)	0.43	57%	<0.001
Serious AIDS events	14	50	0.28	72%	<0.001
Serious Non-AIDS events	29	47	0.61	39%	0.04
Deaths	12	21	0.58	42%	0.13
Cancer	14	39	0.36	64%	0.001

Rates and RR of event were lower in the immediate vs deferred treatment group irrespective of:

- Latest CD4 cell count
- Age, gender, race, geographic region (high vs Low/Mod income)
- Baseline CD4+, Baseline HIV RNA, smoker or FR 10 year CHD risk

Summary:

- Starting ART immediately vs deferring until CD4 count is <350 cells/mm^3 results in a 57% reduction in risk of primary outcome

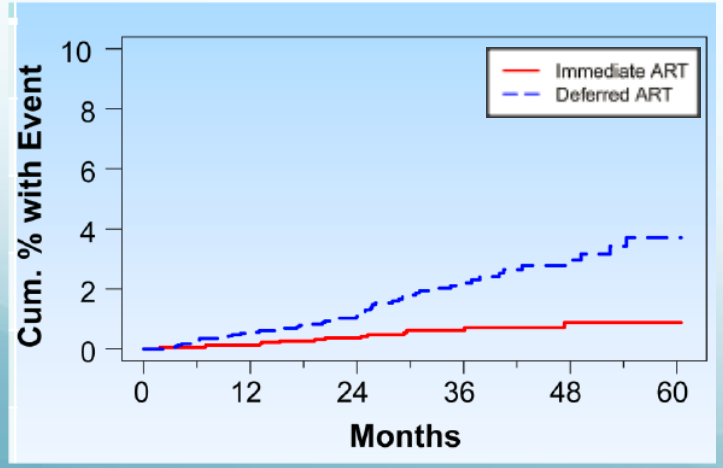
Types of event

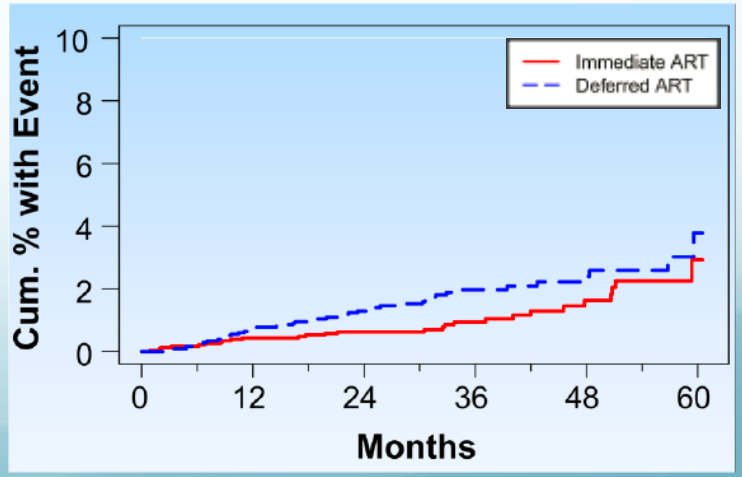
AIDS event	Imm. ART	Def. ART
TB, pulm or extrapulm.*	6	20
Lymphoma, HL or NHL	3	10
Kaposi's sarcoma	1	11
PCP	1	5
Herpes zoster, diss.	0	3
Other**	3	16
Any serious AIDS	**14**	**50**

* Participants from Africa: 16/26 (62%) of TB cases
** Cervical carcinoma, extra-pulm. cryptococcosis, CMV, recurrent bacterial pneumonia

Non-AIDS event	Imm. ART	Def. ART
Cancer, non-AIDS*	9	18
Cardiovascular disease*	12	14
Liver or renal disease	1	2
Death, other	7	13
Any serious non-AIDS	**29**	**47**

* Participants from Australia, Europe, Israel and USA:
22/27 (81%) cancer cases
19/26 (73%) CVD cases





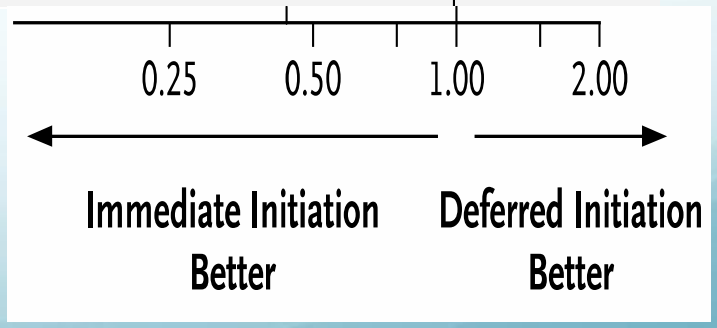
START: key points

- No evidence that benefit of immediate ART differed by age, sex, race, region, CD4, viral load, or risk factors for serious non-AIDS diseases.
- Follow-up ongoing
- Several sub-studies largely show benefit of earlier ART (exception = bone mineral density)
- Low CD4 cell count was not a good predictor of events:
  - Latest CD4 cell count was <350 cells/mm^3 for 4% of follow-up time in the deferred group, five primary events during this time

Lungren, IAS 2015, Oral # MOSY03

Sub-analyses by baseline CD4 and HIV-RNA

Baseline CD4+			
<600 cells/mm^3	31.5	10 (0.44)	35 (1.54)
600–800 cells/mm^3	48.6	24 (0.70)	46 (1.38)
>800 cells/mm^3	19.9	8 (0.63)	15 (1.14)
Baseline HIV RNA			
<5000 copies/ml	31.8	12 (0.56)	18 (0.83)
5000–30,000 copies/ml	35.5	13 (0.53)	36 (1.41)
>30,000 copies/ml	32.5	17 (0.72)	42 (1.92)



Lungren, IAS 2015, Oral # MOSY03

BHIVA 2015

- *"It is important to recognise that despite the significant reduction in relative risk of disease progression with earlier ART, the absolute risk of deferring treatment was small….around 4.1% of individuals in the deferred arm vs 1.5% in the immediate treatment arm experienced a disease progression over 3 years of follow up.* ***The absolute risk of deferring therapy should be considered when making individual decisions.***"

http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf

Starting in individuals with AIDS or a major infection

- We recommend that individuals presenting with an AIDS-defining infection, or with a serious bacterial infection and a CD4 cell count <200 cells/mm^3, start ART within 2 weeks of initiation of specific antimicrobial chemotherapy (1B)

- Recommendation is largely based on ACTG 5164:
  - Fewer AIDS progressions/deaths and improved cost-effectiveness when ART was commenced within 14 days
  - Those with intracranial OI (e.g. cryptococcal meningitis) may be more prone to severe IRIS

Primary HIV infection 1

- We recommend all individuals with suspected or diagnosed PHI are reviewed promptly by an HIV specialist and offered immediate ART [1B]
- Benefits of early ART clear, additional PHI considerations:
  - Often symptomatic
  - Low CD4, high VL (>100k) & short test interval (<12 W since last test) associated with more rapid progression so ART should be prioritised here
  - Individuals should only start when ready to do so; psychologically, immediate ART may have a positive or negative impact

Primary HIV infection 2

- ART should be started when ready in all but should be expedited in the following situations:
  - Neurological involvement (1D)
  - Any AIDS-defining illness (1A)
  - CD4 cell count <350 cells/mm^3 (1C)
  - PHI diagnosed within 12 weeks of a previous negative test (1C)
- Once started, ART should be considered potentially lifelong
- Rationale, pros and cons described in guidelines text

Treatment as prevention 1

- Recommended since 2012
- **Recommendations:**
  - We recommend that ART is offered to all PLWH for the prevention of onward transmission (1A)
  - We recommend the evidence that treatment with ART substantially lowers the risk of transmission is discussed with all PLWH (GPP)
  - An assessment of the risk of transmission to others should be made at diagnosis and subsequent visits (GPP)

TasP: discussion points should include:

- If decision to start is driven primarily by transmission risk it should be the HIV-positive individual's choice
- The clinical benefits of ART at all CD4
- Low risk of tolerability and toxicity issues + option to switch
- Condoms recommended to prevent other STI & unplanned pregnancy
- Once started, ART should generally be continued
- Much for TasP relates to vaginal sex. PARTNER shows benefit for anal sex but the upper estimates for risk are higher
- High and consistent adherence to ART is required
- It usually takes several months to achieve an undetectable viral load in blood after starting ART

SUPPORTING INDIVIDUALS ON ART

Supporting individuals on ART

- We recommend adherence and potential barriers to it are assessed and discussed with PLWH whenever ART is discussed, prescribed or dispensed (GPP)
- We recommend adherence support should address both perceptual barriers (e.g. beliefs and preferences) and/or practical barriers (e.g. limitations in capacity and resources) (GPP)
- Individuals experiencing difficulties with adherence should be offered additional support from staff within the MDT who have experience and/or from organisations offering peer support (GPP)

NICE guidance on adherence

- Summarised in guidelines text
- Important to recognise that non-adherence is common
- Non-judgemental approach
- Make it easier to report by asking routine questions, e.g. number of missed doses over a fixed time period
- Explain why you are asking
- Is the non-adherence:
  - Intentional (due to concerns or problems with meds)
  - Unintentional (due to practical problems)

WHAT TO START

Critical outcomes

OUTCOME	IMPORTANCE
Viral suppression (<50) at W48	9 CRITICAL
Viral suppression (<50) at W96	8 CRITICAL
% with protocol defined VF at W48 +/- W96	8 CRITICAL
% of all randomised subjects with resistance	8 CRITICAL
% discontinuing for AE	8 CRITICAL
% developing G3/4 AE (overall)	7 CRITICAL
% with G3/4 clinical events	7 CRITICAL

http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf

Definitions

- **Preferred:**
  - Strong recommendation that most clinicians and patients would want to follow unless clear rationale not to do so

- **Alternative:**
  - Conditional recommendation and implies an acceptable treatment option for some patients **and might in selected patients be the preferred option**

Specifically apply to ART naïve individuals

http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf

What to start with: BHIVA 2012

	PREFERRED	ALTERNATIVE
NRTI	TDF & FTC	ABC & 3TC[1,3]
3rd agent	ATV/r DRV/r EFV RAL	FPV/r LPV/r NVP[2] RPV[3]

1. ABC contra-indicated if HLA-B*5701 positive
2. NVP contra-indicated in M/F with CD4>400/250
3. Use only recommended if VL <100,000

Williams et al. *HIV Medicine* (2014), **15** (Suppl. 1), 1–85

What to start with: BHIVA 2013

	PREFERRED	ALTERNATIVE
NRTI	TDF & FTC	ABC & 3TC[1,3]
3rd agent	ATV/r DRV/r EFV RAL EVG/COBI	FPV/r LPV/r NVP[2] RPV[3]

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What to start with: BHIVA 2015

	PREFERRED	ALTERNATIVE
NRTI	TDF & FTC	ABC & 3TC[1,2]
3rd agent	ATV/r DRV/r **DTG** EVG/COBI RAL **RPV[3]**	**EFV**

1. ABC contra-indicated if HLA-B*5701 positive
2. ABC/3TC not recommended >100k unless with DTG
3. Use only recommended if VL <100,000

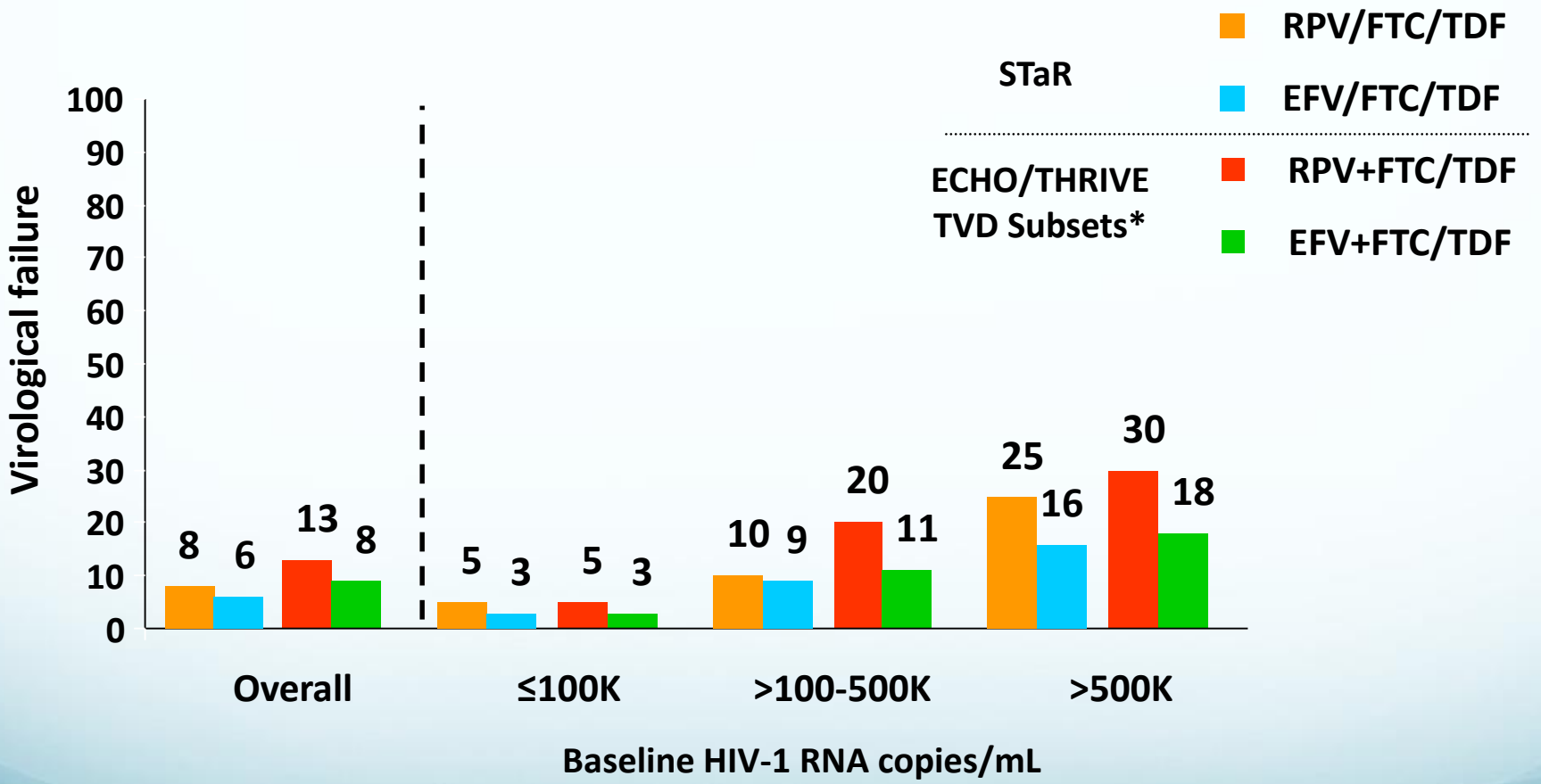
http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf

Why the change? RPV

- RPV moved from alternative to preferred
- Based on a decision to consider RPV within its license, i.e. at baseline VL <100k
- RPV non-inferior to EFV and better tolerated.

http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf

STaR & ECHO/THRIVE
Virological failure at Week 48 per FDA snapshot overall and by baseline HIV-1 RNA

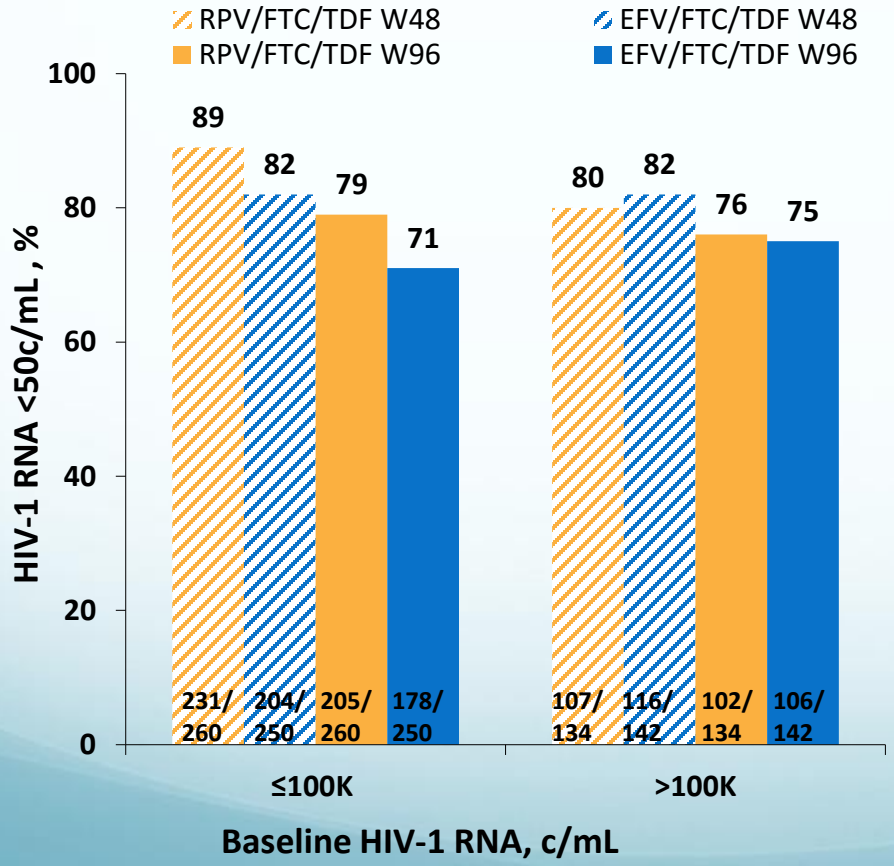


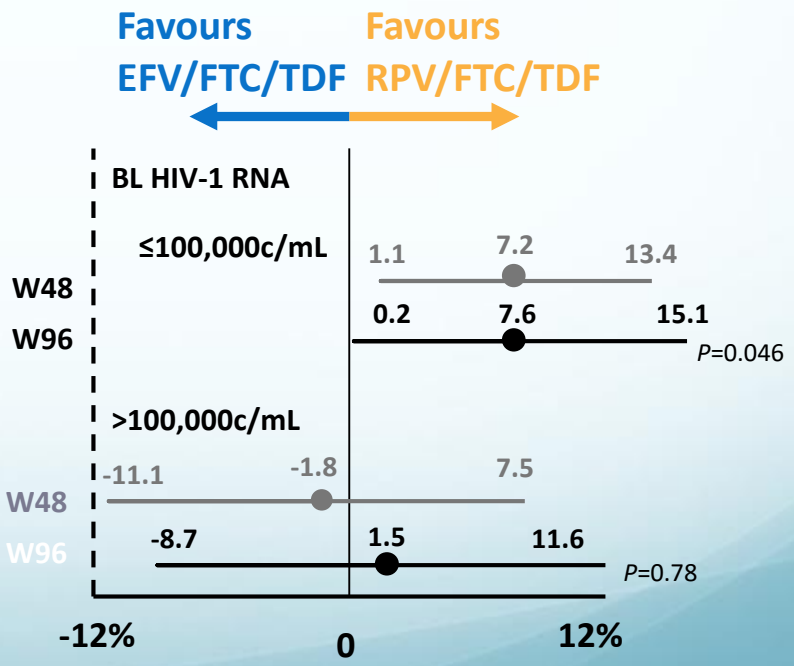
ECHO/THRIVE: Two Phase III double-blinded, double dummy, mulitcenter 96 week studies in treatment-naïve HIV-1 infected subjects randomized to receive either RPV (25mg) or EFV (600mg) in combination with 2 NRTIs (ECHO, FTC/TDF; THRIVE, Investigator's choice [FTC/TDF, n=406; 3TC/AZT, n=204; 3TC/ABC, n=68]). In the pooled TVD subset analysis (N=1096), RPV+TVD was non-inferior to EFV+TVD (HIV-1 RNA <50 c/mL [83%, 81%])

***EVIPLERA Prescribing Information. Gilead Sciences Inc. 2011.**

STaR: week 96
Virological suppression by baseline VL

RPV/FTC/TDF demonstrated a statistically significant difference in efficacy at Week 96 compared to EFV/FTC/TDF in patients with low baseline viral load (≤100k copies/mL)





Why the change? EFV

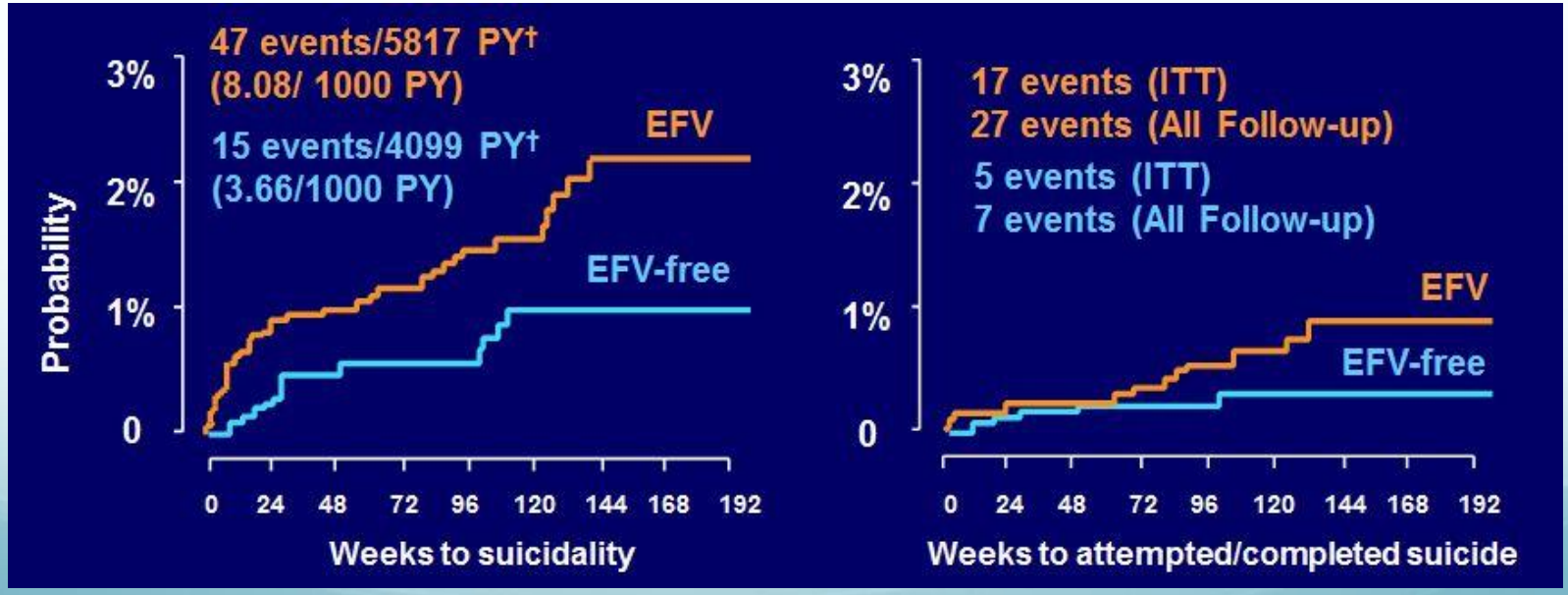
- EFV moved from preferred to alternative
- Better alternatives now available:
  - DTG at primary endpoint in SINGLE
  - RAL after long enough follow-up in STARTMRK
  - RPV in subgroup analysis of StAR
- ACTG suicidality analysis
- Lipids

http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf

ACTG suicidality analysis

ACTG (5095, 5142, 5175, 5202) ARV-naïve studies evaluating associations between patient baseline characteristics and suicide in HIV infected adults from 2001-2007, N=5,332

	HR (95%CI)	P-value
Suicidality – ITT	2.28 (1.27 – 4.10)	0.006
Attempted/Completed Suicide **– ITT** **– All Follow-up***	 2.58 (0.94 – 7.06) 2.6 (1.1 – 5.9)	 0.06 0.03

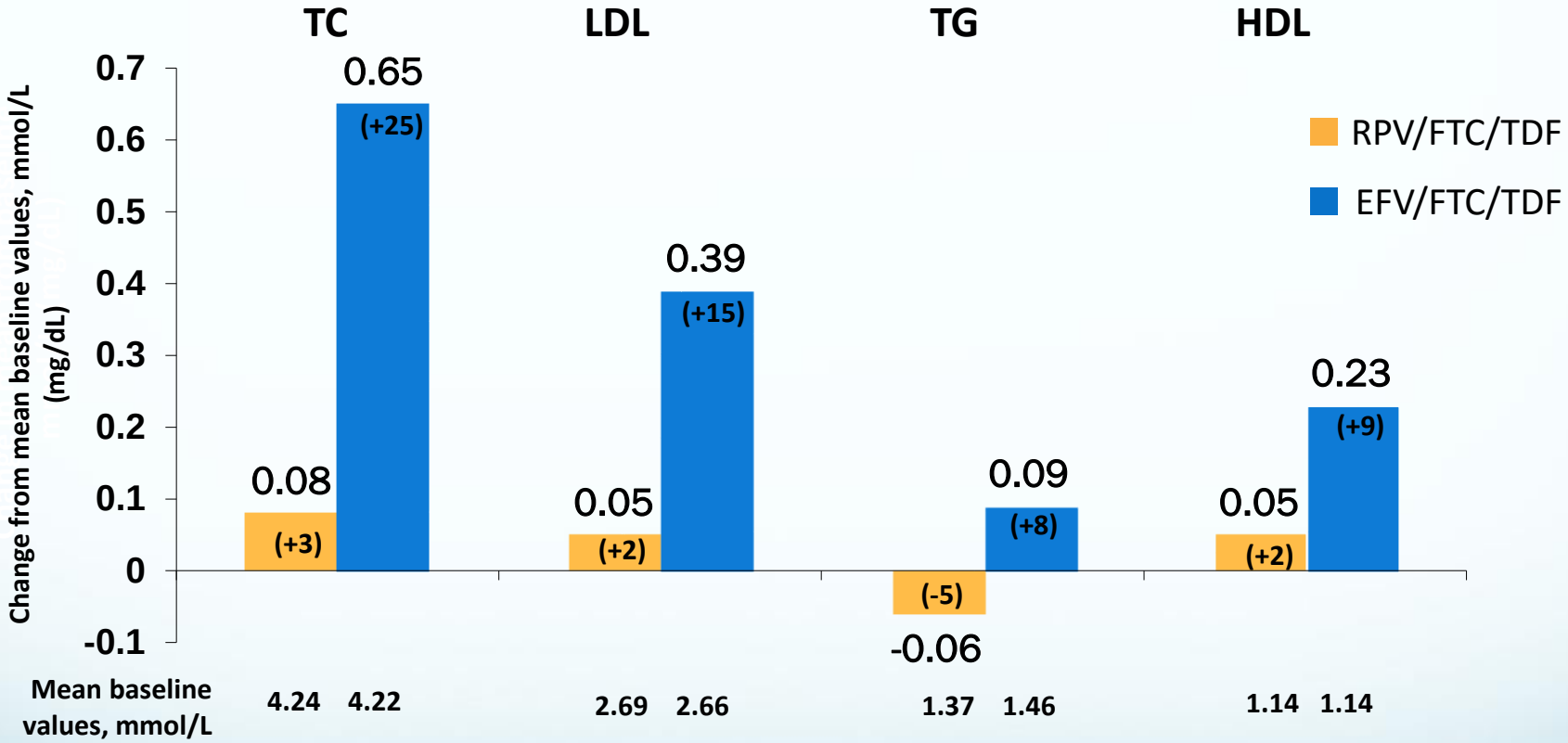


† Person-years, sum of at-risk follow-up

* Includes follow-up beyond DSMB decisions for A5095 and A5175

Mollan K, et al. ID Week 2013. San Francisco, CA. Oral #670

STaR: changes from baseline to week 96 in fasting lipids



- **Change in TC: HDL at Week 96 was –0.2 in both arms**
- **Changes to lipid lowering therapy from baseline:**
  - RPV/FTC/TDF 2.3% vs EFV/FTC/TDF 4.1%

P<0.001 for TC, LDL, HDL and *P*=0.09 for TG, using ANOVA analysis

TC = total cholesterol
LDL = low-density lipoprotein
TG = triglycerides
HDL = high-density lipoprotein

Why the change? NVP, fAPV/r, LPV/r

- NVP
  - Small risk of significant hepatic/cutaneous toxicity not acceptable in light of alternatives
  - People already on it should be reassured
- LPV/r
  - Inferior to EFV, variable associations with CVD and renal impairment, tolerability
  - Still has a role if resistance and cannot have DRV/r
- fAPV/r
  - Similar efficacy and tolerability to LPV/r + risk of rash

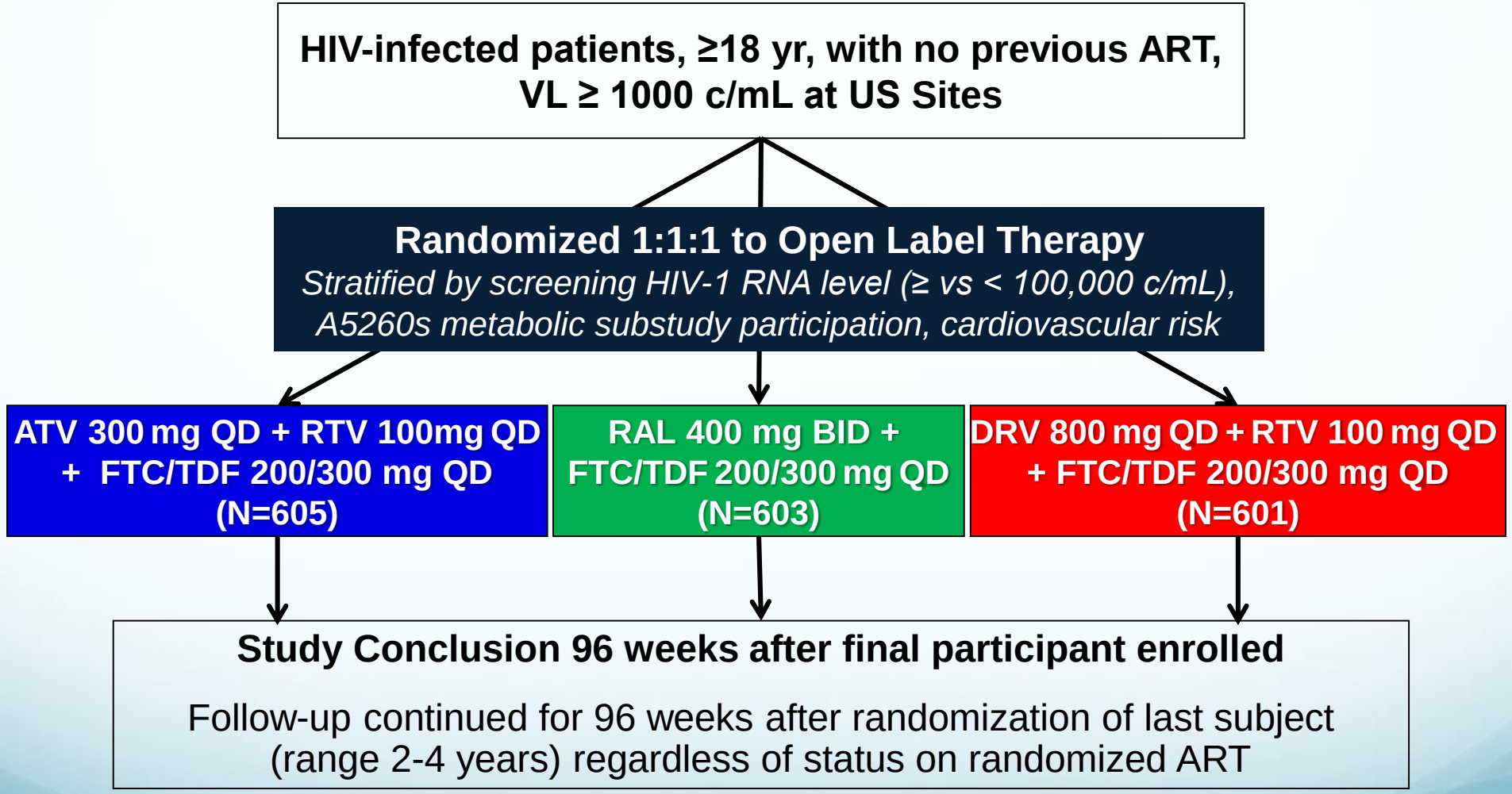
http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf

Why not a change? ATV/r

- DHHS downgraded ATV/r from preferred status
- Decision based mainly on ACTG 5257 results
  - Atazanavir/ritonavir inferior to darunavir/ritonavir and raltegravir by combined endpoint of virological failure + tolerability failure

http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf

A5257 Study Design*



With the exception of RTV, all ART drugs were provided by the study

Landovitz L, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 85.

ACTG 5257: failures

Virologic failure			
Arms	Difference	97.5% CI	Favours
ATV/r vs RAL	3.4%	-0.7%, 7.4%	Equivalent
DRV/r vs RAL	5.6%	1.3%, 9.9%	Equivalent
ATV/r vs DRV/r	-2.2%	-6.7%, 2.3%	Equivalent

Tolerability failure			
Arms	Difference	97.5% CI	Favours
ATV/r vs RAL	13%	9.4%, 16%	RAL superior
DRV/r vs RAL	3.6%	1.4%, 5.8%	Equivalent
ATV/r vs DRV/r	9.2%	5.5%, 13%	DRV/r superior

Cumulative failure			
Arms	Difference	97.5% CI	Favours
ATV/r vs RAL	15%	10%, 20%	RAL superior
DRV/r vs RAL	7.5%	3.2%, 12%	RAL superior
ATV/r vs DRV/r	7.5%	2.3%, 13%	DRV/r superior

Landovitz L, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 85.

ACTG 5257: toxicity discontinuation

	ATV/r (*N*=605)	RAL (*N*=603)	DRV/r (*N*=601)
Any toxicity discontinuation	95 (16%)	8 (1%)	32 (5%)
Gastrointestinal toxicity	25	2	14
Jaundice/hyperbilirubinemia	47	0	0
Other hepatic toxicity	4	1	5
Skin toxicity	7	2	5
Metabolic toxicity	6	0	2
Renal toxicity (all nephrolithiasis)	4	0	0
Abnormal chem/haeme (excl. LFTs)	0	0	2
Other toxicity	2	3	4

Landovitz L, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 85.

Guidelines view of ATV/r

- Non-inferior to Stribild in GS-103
- Non-inferior to DRV/r and RAL by virological endpoint in ACTG 5257
- Jaundice is reversible
- Text stated that jaundice can be distressing and potentially stigmatising so individuals should be offered an alternative to start or switch to if this is the case

http://www.bhiva.org/documents/Guidelines/Treatment/2015/2015-treatment-guidelines.pdf

NEW STRATEGIES and SPECIAL POPULATIONS

Novel strategies

- We recommend against the use of **PI monotherapy** as initial therapy for treatment-naïve patients (1C)
- We suggest the use of **darunavir/r-based dual ART regimen with raltegravir** in treatment-naïve patients with CD4 count >200 cells/mm^3 and VL <100,000 copies/mL where there is a need to avoid abacavir and/or tenofovir (2A)
- We recommend against the use of **PI-based dual ART with a single NNRTI, NRTI or CCR5 receptor** antagonist for treatment-naïve patients (1B)

Novel strategies

- We recommend against the use of **PI monotherapy** for routine ART (1A)
- We recommend against the use of **PI monotherapy** for individuals whose initial regimen has failed or who have established resistance to one more antiretroviral drugs (1A)
- We suggest a **boosted PI plus lamivudine** as an alternative to three-drug ART in individuals with viral suppression (2A)

Special populations

- Tuberculosis
- HBV/HCV co-infection
- HIV-related cancers
- HIV-associated NCI
- Chronic kidney disease
- Cardiovascular disease
- Mental health
- Bone disease

- New sections on
  - Women
  - Adolescents
  - Bone disease
  - Later life

Dosing in renal impairment

Protease Inhibitors			
Antiretroviral	**Usual adult dose**	**Considerations for renal impairment**	**Considerations for haemodialysis**
Atazanavir (Reyataz® hard capsules)	300 mg once daily taken with ritonavir 100 mg once daily	No dosage adjustment is needed for atazanavir in renal impairment	Atazanavir use in haemodialysis patients is not recommended. Atazanavir pharmacokinetic parameters ↓30%- 50% in patients undergoing haemodialysis compared to patients with normal renal function.
Darunavir (Prezista® tablets) (Rezolsta® tablets: DRV 800mg/cobicistat 150mg)	• ART-naïve patients: 800mg once daily with cobicistat 150mg once daily or ritonavir 100mg once daily • ART-experienced patients with no darunavir resistance, with plasma HIV-1 RNA < 100,000 copies/ml and CD4 cell count ≥100: 800mg once daily with cobicistat 150mg once daily or ritonavir 100mg once daily • All other ART-experienced patients: 600mg twice daily with ritonavir 100mg twice daily	No dose adjustment is required for darunavir/ritonavir in patients with renal impairment	As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis. No special precautions or dose adjustments are required
		Cobicistat inhibits the tubular secretion of creatinine and may cause modest declines in creatinine clearance. Hence, the use of creatinine clearance as an estimate of renal elimination capacity may be misleading. Cobicistat as a pharmacokinetic enhancer of darunavir should, therefore, not be initiated in patients with creatine clearance <70 ml/min if any co-administered agent requires dose adjustment based on creatinine clearance: e.g. emtricitabine, lamivudine, tenofovir. Based on the very limited renal elimination of cobicistat and darunavir, no special precautions or dose adjustments of REZOLSTA are required for patients with renal impairment.	Cobicistat has not been studied in patients receiving dialysis, and, therefore, no recommendation can be made for the use of darunavir/ cobicistat in these patients.
Fosamprenavir (Telzir® film coated tablets)	700 mg fosamprenavir twice daily with 100 mg ritonavir twice daily	No dose adjustment is considered necessary in patients with renal impairment	No specific recommendation
Indinavir (Crixivan® hard capsules)	800 mg every 8 hours. Or 400 mg in combination with ritonavir 100 mg, both twice daily	Safety in patients with impaired renal function has not been studied; however, <20% of indinavir is excreted in the urine unchanged, or as metabolites. NB. See summary of product characteristics for details on nephrolithiasis risk	No specific recommendation
Lopinavir (with	400/100 mg (two 200/50	Since the renal clearance of lopinavir and ritonavir is negligible,	Because lopinavir and ritonavir are highly

Food considerations

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Food Considerations for Antiretrovirals

Charts revised May 2015 by www.hiv-druginteractions.org

KEY: With or without food | On an empty stomach | With food

			and potentially reduced therapeutic effect.

Entry/Integrase inhibitors			
Drug		**Usual Adult Dose (UK)**	**Food Considerations**
	Dolutegravir Tivicay® (DTG)	50 mg once daily or 50 mg twice daily depending on comedications or INSTI-resistance	*In the absence of integrase class resistance:* **Can be taken with OR without food** *In the presence of integrase class resistance:* **DTG should preferably be taken with food to enhance exposure, particularly in patients with Q148 mutations.** Food increased the extent and slowed the rate of absorption of dolutegravir. Bioavailability of dolutegravir depends on meal content: low, moderate, and high fat meals increased dolutegravir AUC by 33%, 41%, and 66%, increased Cmax by 46%, 52%, and 67%, prolonged Tmax to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively. These increases may be clinically relevant in the presence of certain integrase class resistance.
	Elvitegravir Vitekta® (EVG)	85 mg or 150 mg once daily depending on coadministered ritonavir-boosted PI	**Must be taken with food** Relative to fasting conditions, administration of elvitegravir as the fixed-dose combination (Stribild®)with food increased EVG Cmax and AUC by 22% and 36% with a light meal (approximately 373 kcal, 20% fat), and by 56% and 91% with a high-fat meal (approximately 800 kcal, 50% fat), respectively.
	Maraviroc Celsentri® (MVC)	150 mg, 300 mg or 600 mg twice daily, depending on interactions with co-administered medicinal products	**Can be taken with OR without food** Administration with a high fat breakfast reduced maraviroc Cmax and AUC by 33%. There were no food restrictions in the studies that demonstrated the efficacy and safety of maraviroc, therefore it can be taken with or without food at recommended doses
	Raltegravir Isentress® (RAL)	400 mg administered twice daily	**Can be taken with OR without food** Raltegravir was administered without regard to food in pivotal safety and efficacy studies. Administration of multiple doses following a moderate-fat meal did not significantly affect raltegravir AUC, with an increase of 13% relative to fasting. Raltegravir C12 hr was 66% higher and Cmax was 5% higher following a moderate-fat meal compared to fasting. Administration following a high-fat meal increased AUC and Cmax ~2-fold and increased C12 hr 4.1-fold. Administration following a low-fat meal decreased AUC and Cmax by 46% and 52%, respectively. Food appears to increase pharmacokinetic variability relative to fasting.

Virological failure: definitions

- **Virological suppression:** achieving and maintaining VL <50 copies/mL
- **Virological failure:** incomplete virological response after commencing treatment or confirmed rebound to CD4 cell count >200 cells/mm^3
- **Incomplete virological response:** two consecutive VL >200 copies/mL after 24 weeks and never <50 copies/mL. Consider baseline VL and regimen (some regimens take longer to suppress). If high baseline viral load (e.g. >100,000 copies/mL) may take longer for viral load to fall
- **Virological rebound:** failure to maintain a VL < limit of detection (ordinarily <40–50 copies/mL) on ≥2 consecutive occasions
- **Low-level viraemia:** persistent VL between 50 and 200 copies/mL
  Virological blip: after virological suppression, a single VL 50–200 copies/mL followed by an undetectable result.

Virological failure: recommendations

- A single VL 50–200 copies/mL preceded and followed by an undetectable VL is usually not a cause for clinical concern (GPP). It should necessitate clinical vigilance, adherence reinforcement, check for possible interactions, and repeat testing within 2–6 weeks depending on ARV regimen
- We recommend that a single VL >200 copies/mL is investigated further, including a rapid re-test +/- genotypic resistance test, as it may be indicative of virological failure (1C)
- We recommend that in the context of low-level viraemia or repeated viral blips, resistance testing be attempted (1D)

Best practice management:
Virological failure

Box 7.1. Best practice for the management of individuals with suspected or confirmed virological failure

- Factors affecting adherence and drug exposure, including tolerability/toxicity issues, drug–drug interactions/food interactions, ARV potency, significant renal/liver disease and mental health/drug dependency problems are evaluated.
- Resistance testing is performed while on failing therapy or within 2–4 weeks of discontinuation.
- Past ART and resistance tests are reviewed for archived mutations.
- Tropism testing is performed if maraviroc is being considered.
- Intensification with a single additional active ARV is not recommended.
- Once virological failure is confirmed and preferably after a resistance-test result is available, the regimen is changed as soon as possible to avoid accumulation of resistance mutations.

The choice of the new ART regimen will primarily depend on the results of resistance testing, prior treatment history and the individual's preference. Additional considerations include the results of tropism and HLA-B*5701 testing, drug–drug interactions/food interactions, co-morbidities and future therapy options. The goal of the new combination is to re-establish a VL <50 copies/mL.

Best practice management:
three-class virological failure

Box 7.2. Best practice for the management of individuals with three-class virological failure

- In individuals with ongoing viraemia and with few options to construct a fully suppressive regimen, referral for specialist advice and/or discussion in a multidisciplinary team 'virtual' clinic is imperative.
- In those with significant resistance, include at least two and preferably three fully active agents with at least one active PI/r (preferably darunavir/r) and one agent with a novel mechanism of action (preferably integrase inhibitor, CCR5 antagonist or fusion inhibitor).
- Treatment interruption is not recommended.

Typical resistance patterns at VF

Box 7.3. Typical resistance patterns on virological failure

- No resistance (wild-type virus)
- Lamivudine/emtricitabine resistance (M184V/I) following any first-line therapy, including tenofovir/emtricitabine or abacavir/lamivudine.
- NNRTI resistance (e.g. K103N, Y181C/I/V or E138K) and/or lamivudine/emtricitabine resistance (following first-line therapy with an NNRTI-based regimen, including tenofovir/emtricitabine or abacavir/ lamivudine).
- INI resistance (e.g. Y143C/R, Q148R/H or N155H) and/or lamivudine/emtricitabine resistance (following first-line therapy with raltegravir or elvitegravir-based regimens, including tenofovir/emtricitabine or abacavir/lamivudine).
- Extended reverse transcriptase resistance (e.g. K65R/L74V or thymidine analogue mutations) (following suboptimal regimens/individuals with more extensive NRTI-based drug history associated with virological failure).
- Three-class resistance (usually NRTI, NNRTI and PI) (following multiple failing regimens).
- Limited or no therapeutic options (following multiple failing regimens, including integrase and R5 inhibitors).

Recommendations:
no or limited drug resistance

- VF on 1st-line ART with wild-type at baseline and no emergent resistance, switch to a PI/r-based combination ART regimen is preferred (1C)
- VF on 1st-line ART with wild-type at baseline and limited emergent resistance (including two-class NRTI/NNRTI), switch to a new PI/r + at least one, preferably two, active drugs (1C)
- VF on first-line PI/r + 2-NRTI, with limited major PI mutations, switch to new active PI/r + at least one, preferably two, active agents, one with novel mechanism of action (1C)
- We recommend against switching a PI/r to an INI or NNRTI as the third agent in individuals with historical or existing reverse transcriptase mutations associated with NRTI resistance or past virological failure on NRTIs (1B)

Recommendations:
multiple class VF +/- extensive drug resistance

- Persistent viraemia and limited options should be discussed/referred for expert advice (including virtual clinic referral) (GPP)
- We recommend individuals with extensive drug resistance are switched to a new regimen of at least two and preferably three fully active agents with at least one active PI/r (such as DRV/r) + one agent with a novel mechanism (INI, MVC or T20) with ETR an option based on viral susceptibility (1C)
- We recommend individuals with extensive drug resistance including reduced DRV susceptibility receive DTG as the INI (1C)
- We suggest consideration on an individual basis re inclusion of NRTIs with reduced activity on genotypic testing (2C)
- We recommend all individuals receive intensive adherence support at the start and at regular intervals (GPP)

Recommendations:
limited or no treatment options

- We recommend accessing newer agents via research trials, expanded access and named individual programmes (GPP)
- We suggest consideration re inclusion of NRTIs with reduced activity on genotypic testing will provide additional activity (2C)
- We recommend against discontinuing or interrupting ART (1B)
- We recommend against adding a single, fully active ARV because of the risk of further resistance (1D)
- We recommend against the use of maraviroc to increase the CD4 cell count when there is evidence for X4 or dual tropic virus (1C).
- We recommend that in the context of triple-class failure with RAL/EVG selected integrase resistance, BD DTG should be included where there is at least one fully active agent in the background regimen (1C).

Thank you!

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