BHIVA Treatment Guidelines

2012 plus 2013 update

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Overview

- Guideline development process
- Updated sections:
  - When to start
  - Primary HIV infection
  - What to start
  - Managing virological failure
- New/extended sections
  - Treatment to reduce transmission
  - Novel ART strategies
  - Special populations
  - HIV in women

Background

Scope and purpose

- To provide guidance on best clinical practice in the treatment and management of adults with HIV infection with antiretroviral therapy (ART)
- Aimed at clinical professionals directly involved with and responsible for the care of adults with HIV infection and at community advocates responsible for promoting the best interests and care of HIV-positive adults
- Should be read in conjunction with other published BHIVA guidelines

Guideline development process

- Updated by BHIVA in 2011
- Use of **GRADE** (Grading of Recommendations Assessment, Development and Evaluation)[1,2]
- Scope, purpose & topics agreed by writing panel
- Questions drafted by panel then literature review performed by an information scientist
- Literature search:
  - Medline, Embase & Cochrane library 01/2008 to 09/2011
  - Abstracts from selected conferences 01/2009-09/2011
  - Limited further searches concerning specific third agents (rilpivirine [RPV] and elvitegravir [ELV]/cobicistat [COBI]) covering the period from 09/2011 carried out in 2013

[1] Guyatt GH et al. BMJ 2008; 336: 1049–1051. [2] The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) Working Group. www.gradeworkinggroup.org

Guideline development 2

- For key questions, GRADE evidence profile and summary of findings tables were constructed, using **predefined and rated** treatment outcomes (listed in appendices) to:
  - Help achieve consensus
  - Aid transparency
- Prior to final approval:
  - On line public consultation
  - External peer review commissioned.

Patient involvement and consultation

- Patient involvement
  - Two committee reps (elected by UK CAB)
  - Two patient & community representative meetings
- Transparency
  - Guidelines scrutinised extensively during consultation process
  - Many comments by clinicians, patients, policy makers and pharmaceutical companies

Grading system

Recommendations

- 3 main groups:
  - Grade 1
  - Grade 2
  - Good practice point (GPP)

Grade 1 recommendation

- Strong recommendation to do/not do something
- Benefits > risks (or vice versa) for most patients
- Most clinicians and patients should and would want to follow this unless clear rationale for alternative approach
- *"**We recommend**"*

Grade 2 recommendation

- Weaker or conditional
- Risks & benefits more closely balanced or uncertain
- Most clinicians and patients would want to follow it but many would not
- Alternatives may be reasonable depending on the individual
- *"**We suggest**"*

Quality of evidence

Grade A

high-quality; consistent results from good RCTs, or v strong evidence of another sort (e.g. well-executed v robust observational studies)

Quality of evidence

Grade B

moderate-quality from randomised trials with serious flaws or other study designs (e.g. Good observational studies with consistent effects)

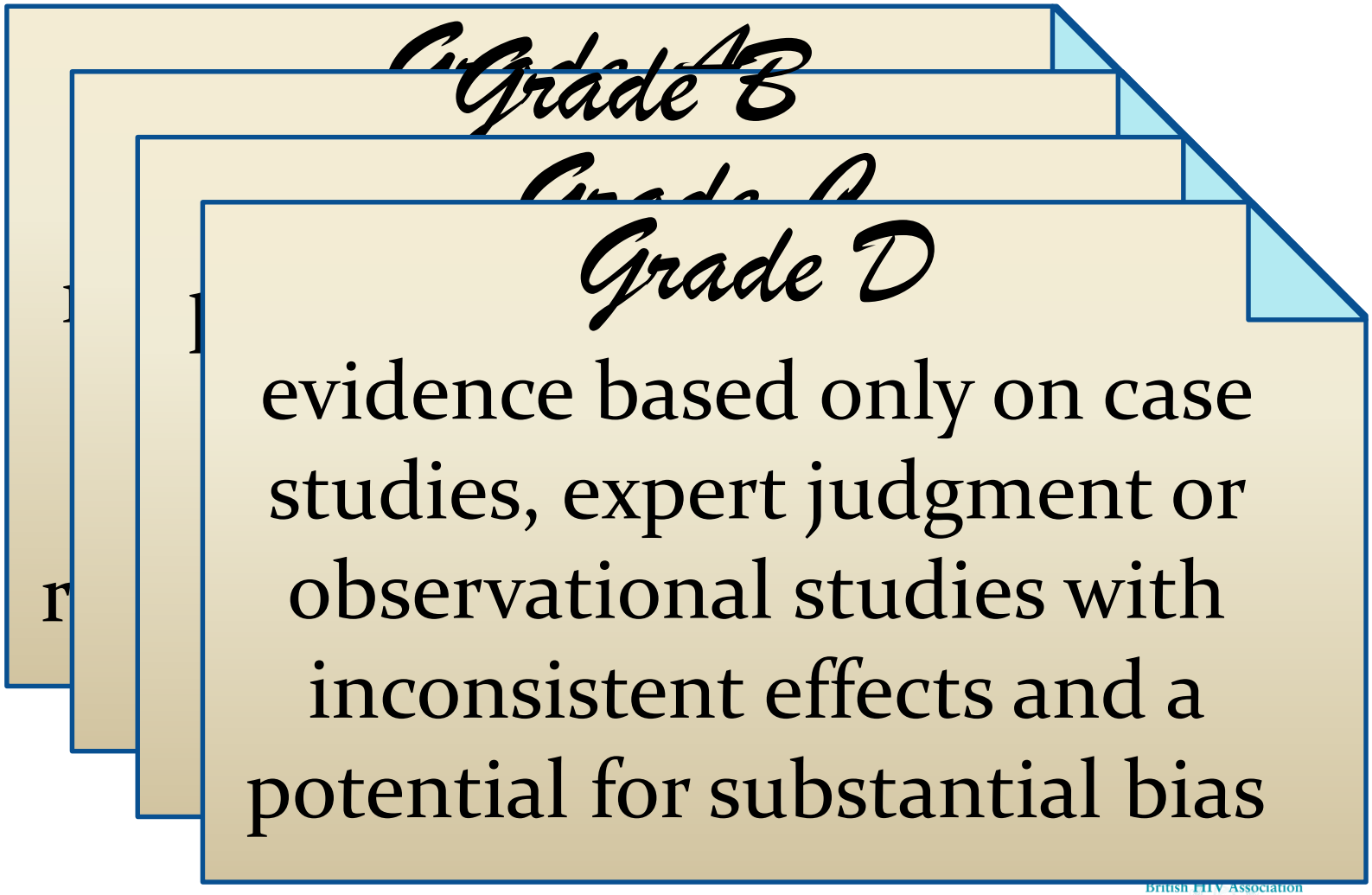
Quality of evidence

Grade B

Grade C

low-quality; from controlled trials with several serious limitations or good observational studies with limited evidence on effects

Quality of evidence



Good practice point

- Based on clinical judgment & experience
- Emphasise an area of important clinical practice with no significant research & none likely
- Address an aspect of treatment and care regarded as such sound clinical practice that health care professionals unlikely to question it and alternative is deemed unacceptable

Additional points

Aims of treatment

- Primary aim to prevent chronic HIV-associated mortality & morbidity at low cost of drug toxicity
- Improve physical & psychological well-being of PLWH
- A further aim is reduction in sexual transmission of HIV and for some patients may be the primary aim

Cost effectiveness data: not included as an outcome

- Cost of drugs major factor in treatment/care costs
- Generic drugs and standard HIV tariff (England) raise difficult choices about value of different ARV drugs
- Limited UK cost-effectiveness data for different ARV drugs so cost-effectiveness **not** an outcome in ART comparisons
- Better outcomes (efficacy, toxicity, resistance) likely beneficial impact on long-term cost-effectiveness and resource use
- If equivalent efficacy, determining an acceptable threshold at which differences in toxicity, tolerability and convenience outweigh cost/resource differences will be important and these thresholds may differ amongst clinicians and patients alike

Cost 2

- Commissioning arrangements and local drug costs will and should influence ART choice where outcomes otherwise equivalent
- Reducing treatment costs should not be at the cost of an increased risk of poorer treatment outcomes and quality of care, not least as these are likely to have a detrimental impact on long-term cost

When to start

When to start 2012

- **We recommend starting ART in patients:**
  - With chronic HIV & ≤350 [1A] (Consider earlier if older)
  - With the following conditions:
    - AIDS [1A], HIV-related co-morbidity [1C], HBV [1B] and HCV [1C] if the CD4 count is ≤500, nADM requiring immunosuppressive radiotherapy or chemotherapy [1C]
- **We suggest starting ART in patients:**
  - With HBV & CD4 >500 + HBV treatment indicated [2B]

When to start 2013: hepatitis B and HIV coinfection

HIV/HBV coinfection	RECOMMEND
CD4 <500	Fully suppressive ART including anti-HBV active antivirals
CD4 >500 **AND/OR** • HBV-DNA >2000 IU/ml • Evidence of more than minimal fibrosis (Metavir >F2)	Fully suppressive ART including anti-HBV active antivirals

When to start 2013: hepatitis C & HIV coinfection

	RECOMMEND	SUGGEST
All patients	Assess for HCV Rx	
CD4 <350	ART to allow immune recovery before HCV Rx	
CD4 350-500	ART when CD4 <500 in all who are not to start HCV Rx immediately ART to optimise immune status before HCV Rx when CD4 350-500 unless HCV Rx urgent (start ART once stable on HCV Rx)	
CD4 >500		ART in all who are not to start HCV Rx immediately

Rx = treatment

Why not earlier?

- No completed RCT of >350 vs >500
  - START results expected 2016
- Cohorts: Lead time bias, not RCT, CASDADE benefit >500 but ?representative
- SMART showed benefit. Deferred arm <250
- 2013 update adds discussion but recommendation unchanged
- Clinicians should not delay if CD4 close to but above 350

When to start: UK focus

"The BHIVA treatment guidelines were developed primarily with patients from the UK in mind. In other settings, where there are particularly high TB rates, constraints on delivery of care, and high losses through the care and treatment cascade, earlier ART initiation may be more important to increase retention of patients in care after diagnosis"

When to start: OI

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

When to start in OI: rationale

- **Largely based on ACTG 5164:**
  - Fewer AIDS progressions/deaths and improved cost-effectiveness if ART within 14 days (median 12) vs ART post completion of OI treatment (median 45)
  - TB excluded; majority had PCP, followed by cryptococcal meningitis (CM) & bacterial infections
  - Patients well enough for informed consent and oral medications, so findings may not be generalizable if severely unwell or requiring ITU
- Observational data suggest survival benefit if ART started on ITU (insufficient for a recommendation)

When to start: OI

- No increase in immune reconstitution disorders (IRD) or adverse events with early ART in ACTG 5164 but intracranial OI may be more prone to severe IRDs
- Some data suggest that caution should be exercised with CM:
  - Two studies from sub-Saharan Africa show increased mortality with early ART but very different healthcare settings and, in one, non-preferred antifungal regimen.
  - In The COAT study acellular CSF and decreased Glasgow Coma Scale particularly associated with increased mortality with early ART

Primary infection: when to start

- **Recommend:**
  - Neurological involvement [1D]
  - AIDS defining illness [1A]
  - Confirmed CD4 <350 [1C]
- **Suggest (in text) discuss pros and cons of ART if:**
  - Short test interval (≤12 weeks from a negative HIV Ab test) particular, those with severe symptoms of seroconversion such as rash, fever, weight loss, persistent lymphadenopathy, diarrhoea >4 days, malaise, headaches or laboratory evidence of acute HIV infection

"most clinicians, would recommend that once started treatment should be continued indefinitely"

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Treating in PHI: rationale

- **Scientific rationale as follows:**
  1. Preservation of specific anti-HIV CD4 T lymphocytes that would otherwise be destroyed by uncontrolled viral replication, the presence of which is associated with survival in untreated individuals
  2. Reduction in morbidity associated with high viraemia and profound CD4 cell depletion during acute infection
  3. Reduction in the enhanced risk of onward transmission of HIV associated with PHI

Treating in PHI: discussion points

1. 48 (not 12) weeks ART delayed CD4 decline and lowered viral set point up to 60 weeks after cessation; no clear evidence of long-term benefit
2. No study examining if ART should continue long term
3. Discontinuation of ART in the context of treatment of PHI was not commonly associated with morbidity
4. No specific evidence to support ART in PHI for TasP but is little reason to consider it any less effective
5. Patients with PHI may particularly vulnerable psychologically, thus ill- prepared to commit to starting long-term treatment.

Primary infection: when to start

- **Issues:**
  - Psychological state of patient
  - Definition of acute PHI (<3 vs 6 months)
  - Impact of more frequent HIV testing on earlier identification of HIV disease
  - Severe symptoms (including but not limited to neurological) associated with more rapid progression

Treatment to reduce transmission

- **Recommend:**
  - Discuss data with all patients + assess current risk of transmission to others (GPP)
  - Following discussion, if a patient with a CD4 count >350 wishes to start ART to reduce the risk of transmission to partners, this decision is respected and ART is started (GPP)

Evidence

- **Supporting:**
  - Numerous studies correlating transmission risk with viral load
  - HPTN052
- **Concerns:**
  - Very few MSM in HPTN052
  - Is ART as protective wrt anal sex?

TasP: discussion points

- Patient's choice & not due to pressure from others.
- ART lowers, rather than eliminates, risk
- If CD4 >350, uncertain if benefits of immediate ART to their own health will be outweighed by any harm
- Condoms, male & female, still recommended
- Risks with interrupting ART, so once started, it should generally be continued indefinitely.
- The evidence for ART mainly relates to vaginal sex; though highly likely to reduce risk of transmission for anal sex, the residual risk could be higher

TasP: discussion points

- High and consistent adherence to ART is required to maintain viral suppression and minimize transmission risk
- Taking ART does not result in immediate complete viral suppression; it usually takes several months to achieve an undetectable VL in blood
- The use of ART to reduce transmission risk is a particularly important consideration in serodiscordant heterosexual couples wishing to conceive and it is recommended that the HIV-positive partner be on fully suppressive ART

What to start

Methodology in decision making for what to start

- Study outcomes selected and graded by writing panel
- Numerically graded and grouped into:
  - CRITICAL
  - IMPORTANT
  - NOT IMPORTANT

Critical outcomes

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

Important outcomes

OUTCOME	IMPORTANCE
% with G3/4 CNS events	5 IMPORTANT
% with G3/4 diarrhoea	5 IMPORTANT
10% or more limb fat loss	5 IMPORTANT
% change limb fat	5 IMPORTANT
% change trunk fat	5 IMPORTANT
% change visceral adipose tissue	5 IMPORTANT
Change in visceral: total adipose tissue ratio	5 IMPORTANT
Renal impairment	4 IMPORTANT

Not important outcomes

OUTCOME	IMPORTANCE
% with G3/4 total cholesterol events	3 NOT IMPORTANT
% with G3/4 LDL cholesterol events	3 NOT IMPORTANT
% with G3/4 triglycerides	3 NOT IMPORTANT
Total hip BMD decrease 6% or more	3 NOT IMPORTANT
Total spine BMD decrease 6% or more	3 NOT IMPORTANT
Change in lumbar spine BMD	3 NOT IMPORTANT
Change in hip spine BMD	3 NOT IMPORTANT
Bone fractures	3 NOT IMPORTANT

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

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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>400/2
3. Use only recommended if VL <100,000

What to start with: BHIVA 2012

	ATIVE
NRTI	3TC[1,3]
3rd agen	/r
	/r
	D2
	/3

"The presence or future risk of co-morbidities and potential adverse effects need to be considered in the choice of antiretroviral drugs in individual patients"

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

2013 update

- Limited further searches concerning specific third agents covering the period from September 2011:
  - Rilpivirine [RPV]
  - Elvitegravir [ELV]/cobicistat [COBI]

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]

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

What to start: BACKBONE

Backbone: Truvada vs Kivexa

- **We recommend** therapy naïve patients start ART containing TDF & FTC as the backbone (1A)

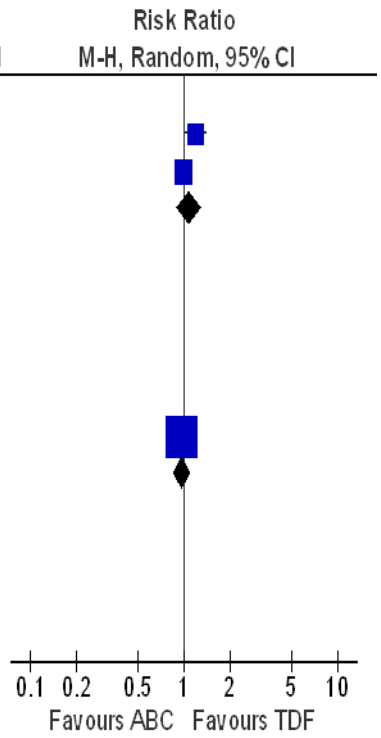
- **We suggest** ABC & 3TC is an acceptable alternative backbone in therapy naïve patients with baseline viral load ≤100,000 (2B)(2A)

Evidence: Truvada vs Kivexa

- **3 RCTs:**
  - ACTG 5205 (n=1858)
  - ASSERT
  - HEAT
- **1 meta-analysis:**
  - Hill (HIV Med 2009)
- Findings & Forest plots summarised in appendix

Forest plot: Truvada vs Kivexa
Viral suppression (<50) at week 48/week 96

Study or Subgroup	TDF/FTC Events	TDF/FTC Total	ABC/3TC Events	ABC/3TC Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 <50 copies at 48 weeks						
Post 2010 (ASSERT)	137	193	114	192	46.0%	1.20 [1.03, 1.39]
Smith 2009 (HEAT)	231	345	232	343	54.0%	0.99 [0.89, 1.10]
Subtotal (95% CI)		538		535	100.0%	1.08 [0.90, 1.30]
Total events	368		346			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.19$, df = 1 (P = 0.04); $I^2 = 76\%$						
Test for overall effect: Z = 0.81 (P = 0.42)						
1.1.2 <50 copies at 96 weeks						
Smith 2009 (HEAT)	200	345	205	343	100.0%	0.97 [0.86, 1.10]
Subtotal (95% CI)		345		343	100.0%	0.97 [0.86, 1.10]
Total events	200		205			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						



No clear difference between the arms;
5202 excluded & quality rated low/very low

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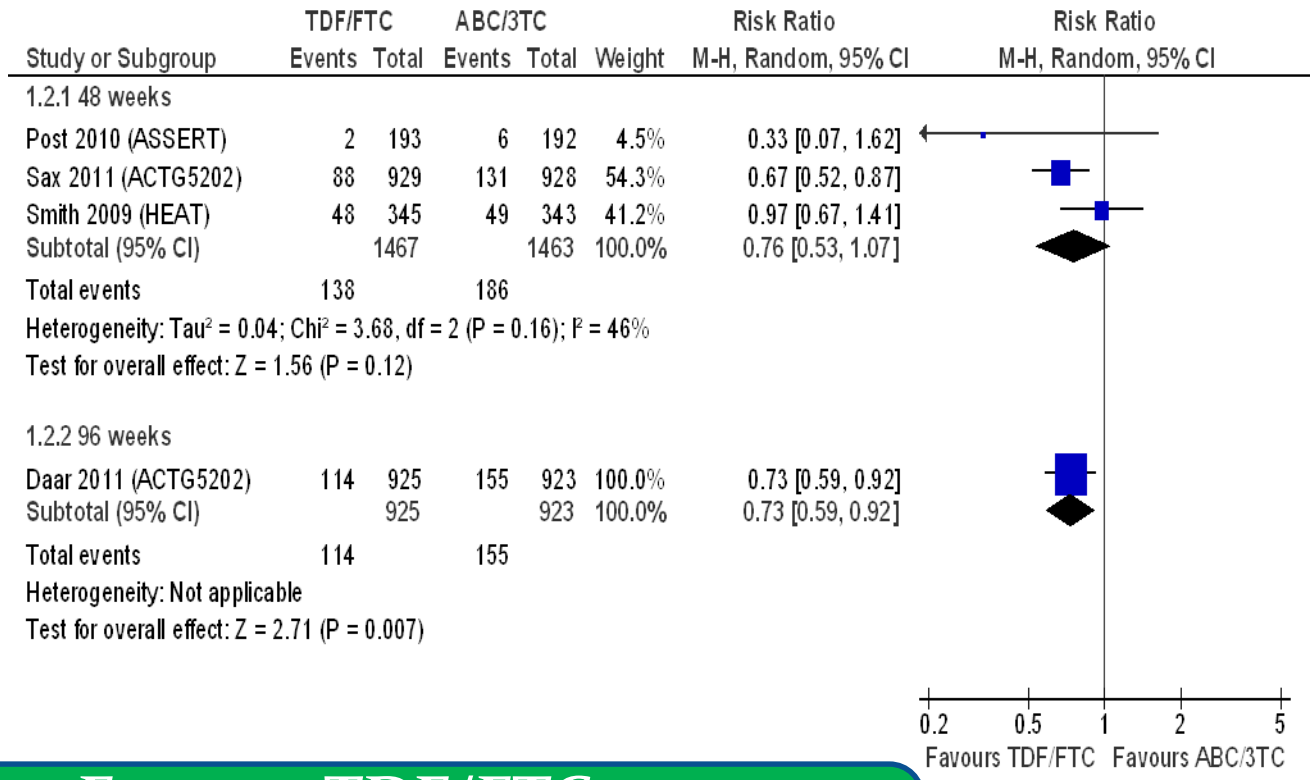
% randomised subjects with protocol-defined VF at week 48 +/-96 weeks



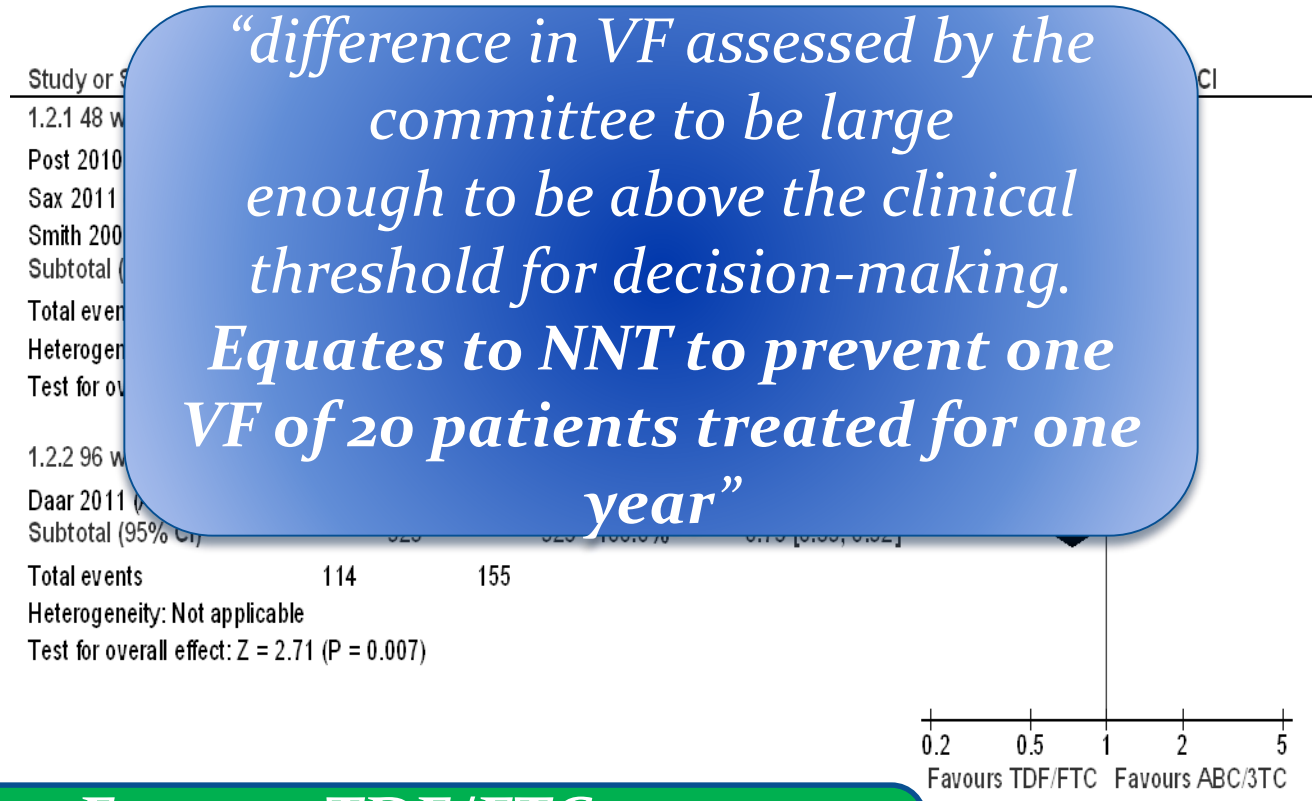
Study or Subgroup	TDF/FTC Events	TDF/FTC Total	ABC/3TC Events	ABC/3TC Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 48 weeks						
Post 2010 (ASSERT)	2	193	6	192	4.5%	0.33 [0.07, 1.62]
Sax 2011 (ACTG5202)	88	929	131	928	54.3%	0.67 [0.52, 0.87]
Smith 2009 (HEAT)	48	345	49	343	41.2%	0.97 [0.67, 1.41]
Subtotal (95% CI)		1467		1463	100.0%	0.76 [0.53, 1.07]
Total events	138		186			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 3.68$, df = 2 (P = 0.16); $I^2 = 46\%$						
Test for overall effect: Z = 1.56 (P = 0.12)						
1.2.2 96 weeks						
Daar 2011 (ACTG5202)	114	925	155	923	100.0%	0.73 [0.59, 0.92]
Subtotal (95% CI)		925		923	100.0%	0.73 [0.59, 0.92]
Total events	114		155			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.71 (P = 0.007)						

Favours TDF/FTC:

NS at W48; sig at W96 (5202) quality rated high

NB. different failure definitions in the 3 trials

% randomised subjects with protocol-defined VF at week 48 +/-96 weeks



"difference in VF assessed by the committee to be large enough to be above the clinical threshold for decision-making. ***Equates to NNT to prevent one VF of 20 patients treated for one year"***

Favours TDF/FTC:

NS at W48; sig at W96 (5202) quality rated high

NB. different failure definitions in the 3 trials

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Truvada vs Kivexa: Other endpoints

- Other important outcomes including resistance, AE discontinuations and lipodystrophy, **no difference**
- No data for QoL outcomes
- G3/4 AE (all) & G3/4 ALT/AST, trends favoured TVD
- Resistance **rates** similar but greater number on ABC-3TC as more cases of VF
- Only outcome that significantly favoured ABC-3TC was **BMD** but no difference in bone fractures was identified

NRTI backbone

- No role for other NRTI backbones except AZT/3TC in some circumstances (eg pregnancy)
- No place for the following as initial therapy:
  - d4T: mitochondrial toxicity
  - ddI: hepatic toxicity

What to start: 3rd agent

What to start with: BHIVA 2008

- EFV should be considered first line (Ib)
- PI/r ordinarily reserved for specific groups of patients, eg. primary resistance, women planning pregnancy and some patients with psychiatric problems (IV).
- NVP alternative to EFV in women planning pregnancy % patients with mental health problems but only within CD_4 restrictions (Ib)

What to start: BHIVA 2008

- EFV only preferred 3rd agent
- Primarily due to ACTG5142 where EFV performed better than LPV/r first line
- New head to head studies since then
- Other 3rd agents compared to EFV
  - Directly or indirectly depending on available trials
  - vs EFV: ATV/r; RAL; RPV; ELV/COBI
  - vs LPV/r: ATV/r; DRV/r
  - vs r/ATV; ELV/COBI

What to start: BHIVA 2012/2013

- We **recommend** therapy-naïve patients start combination ART containing ATV/r, DRV/r, EFV, RAL or ELV/ COBI as the third agent (1A)
- We **suggest** for therapy-naïve patients LPV/r & FPV/r are acceptable alternative PIs, NVP & RPV are acceptable alternative NNRTIs (2A)
- NVP must only be used according to CD4 criteria and RPV should only be used in patients with baseline VL <100 000 copies/mL

EFV vs ATV/r & EFV vs RAL

- ATV/r and RAL compared directly with EFV in RCTs
- For critical virological efficacy/safety outcomes, no differences (evidence rated as high or moderate)
- Difference in resistance rate favouring ATV/r (RR 3.94; $P < 0.00001$) though overall rate low both
- Differences in rate of grade 3/4 CNS events and the rate of lipid abnormalities favouring both ATV/r and RAL. These differences may influence choice for individual patients.

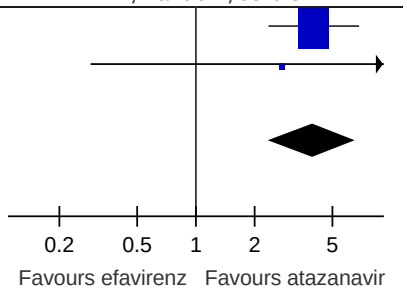
ATV/r vs EFV: 5202 & ALTAIR

Resistance

	Efavirenz		Atazanavir			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Daar 2011 (ACTG 5202)	68	922	17	926	94.9%	4.02 [2.38, 6.78]
Puls 2010 (ALTAIR)	3	114	1	105	5.1%	2.76 [0.29, 26.15]
Total (95% CI)		**1036**		**1031**	**100.0%**	**3.94 [2.37, 6.56]**
Total events	71		18			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.10$, df = 1 (P = 0.75); $I^2 = 0\%$

Test for overall effect: Z = 5.27 (P < 0.00001)

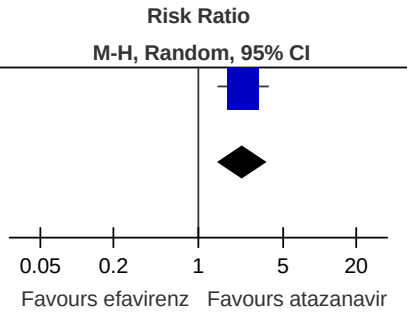


Grade 3/4 neurological event

	Efavirenz		Atazanavir			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Daar 2011 (ACTG 5202)	56	922	24	926	100.0%	2.34 [1.47, 3.75]
Total (95% CI)		**922**		**926**	**100.0%**	**2.34 [1.47, 3.75]**
Total events	56		24			

Heterogeneity: Not applicable

Test for overall effect: Z = 3.56 (P = 0.0004)



20 people would need to be treated with ATV/r rather than EFV to prevent one case of drug resistance

DRV/r vs EFV

- No direct comparisons so compared indirectly
- Some differences between but overall judged insufficient to invalidate an indirect comparison between EFV and DRV/r:
  - DRV/r vs LPV/r (ARTEMIS)
  - LPV/r vs Efavirenz (LAKE, MEXICO, 5142)
  - Differences in:
    - Backbone used
    - Date of recruitment
    - Tablets and capsules

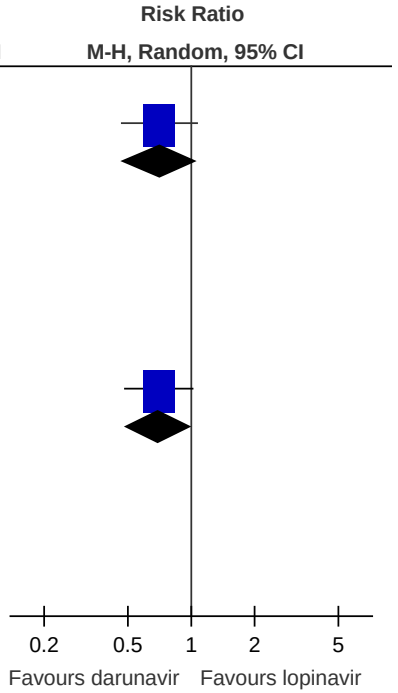
Direct comparisons

- **DRV/r vs LPV/r:**
  - Clinically significant differences in the critical outcomes virological suppression, discontinuation for AE and serious AE in favour of DRV/r
  - No differences in critical outcomes VF & resistance
- **EFV vs LPV/r:**
  - Clinically significant differences in the critical outcomes VF and VS at 96 weeks in favour of EFV
  - No differences in critical outcomes resistance and discontinuation due to adverse events
  - Significant differences in some AE favouring EFV over LPV/r

DRV/r vs LPV/r

Virological failure

Study or Subgroup	Darunavir Events	Total	Lopinavir Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 48 weeks						
Ortiz 2008 (ARTEMIS 48wk)	34	340	49	346	100.0%	0.71 [0.47, 1.07]
Subtotal (95% CI)		**340**		**346**	**100.0%**	**0.71 [0.47, 1.07]**
Total events	34		49			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.66 (P = 0.10)						
4.2.2 96 weeks						
Mills 2009 (ARTEMIS 96wk)	41	343	59	346	100.0%	0.70 [0.48, 1.01]
Subtotal (95% CI)		**343**		**346**	**100.0%**	**0.70 [0.48, 1.01]**
Total events	41		59			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.88 (P = 0.06)						



13 people would need to be treated with DRV/r rather than LPV/r to gain 1 extra person with viral suppression (cf 8 treated with EFV rather than LPV/r for one extra VS)

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EFV vs DRV/r (indirect comparison)

If 1000 people treated with DRV/r rather than LPV/r

- 78 more people with viral suppression
- 45 fewer serious adverse events
- 35 fewer discontinuations due to adverse events.

If 1000 people treated with EFV rather than LPV/r

- 130 fewer people with virological failure
- 28 fewer with grade 3 or 4 diarrhoea
- 39 fewer with grade 3 or 4 triglyceride adverse events.

The choice between EFV & DRV/r therefore depends on the relative weight given to each outcome.

EFV s RPV

- No difference in virological suppression but differences in critical outcomes of drug resistance & VF in favour of EFV
- Pooled analyses show risk of VF on RPV highest in patients with a baseline VL >100 000 copies/mL
- For critical safety outcomes difference in proportion discontinuing for AE in favour of but no difference in serious adverse events
- RPV had better lipid profile outcomes.

EFV vs RPV

- StAR showed overall noninferiority of fixed-dose TDF/FTC/RPV vs TDF/FTC/EFV at 48 weeks
- In a subgroup analysis in patients with baseline viral load <100 000, superiority of the RPV demonstrated
- Like ECHO and THRIVE, StAR confirmed higher VF on RPV at VL >100 000 but not <100 000 copies/mL
- Because RPV licensed for use in patients with baseline VL <100 000 should remain **alternative**

EFV vs RPV

- Fewer neuropsychiatric AE with RPV than with EFV
- RPV may be useful if VL <100 000, where concerns about neuropsychiatric side effects are paramount
- Important patients can both comply with dietary requirements and avoid acid-reducing agents
- Very few data regarding RPV with ABC/3TC backbone

RPV vs EFV

	Efavirenz better	Rilpivirine better	ARR	NNT
Drug resistance	yes	no	40/1000	25
Grade 3 or 4 laboratory AE	no	yes	67/1000	
Grade 3 or 4 ALT	no	yes	19/1000	
Grade 3/4 total cholesterol	no	yes	13/1000	
Grade 3/4 LDL cholesterol	no	yes	29/1000	
Grade 3 or 4 triglycerides	no	yes	19/1000	
Discontinuation for AE	no	yes	43/1000	

25 people would need to be treated with EFV rather than RPV to avoid 1 case of drug resistance. But at expense of more laboratory AE and AE discontinuations

On balance, committee felt VF outweighed others plus RPV only licensed at VL <100,000 hence RPV an alternative

EFV vs elvitegravir/cobi

- Since 2012, FDC of TDF/FTC/ELV/COBI (Stribild) licensed
- Two pivotal studies have compared it to fixed-dose TDF/FTC/EFV (GS-102) and TDF/FTC + ATV/r (GS-103)
- VF rates not reported but discontinuations for 'lack of efficacy' similar in both arms of each study
- Since Stribild non-inferior to both EFV and ATV/r, both preferred agents, Stribild also preferred 1st line
- Stribild may confer some advantages in terms of its toxicity, but multiple potential drug interactions.

Alternatives: other

- **NVP:**
  - Due to CD4 restriction, risk of rash/hepatitis & higher rates of discontinuation for AE
- **LPV/r:**
  - Based on virological outcome vs EFV & DRV/r
- **fAPV/r:**
  - Based in similar virological efficacy to LPV/r

Not recommended: Saquinavir/r

- Non-inferior to LPV/r:
  - Numerically more VF in GEMINI
- Not recommended in guidelines due to:
  - Higher pill burden
  - Availability of alternative PI/r
  - SPC recommends dose escalation and careful ECG monitoring due to QTi prolongation

Fixed dose combinations (FDC): 1

- Only studies comparing same drugs & dose frequency given as combination or separate pills were considered
- No meta-analyses for ART
- Meta-analysis of 9 RCTs/cohorts in a range of diseases found FDCs associated with significant reduction in risk of non-adherence1
- A meta-analysis of cohort studies found FDCs for antihypertensives associated with increased adherence but no improvement in the control of blood pressure2
- Retrospective pharmacy database study found no benefit in persistence on 1st-line ART for any FDC over separate agents3

1. Bangalore S *et al. Am J Med* 2007; **120:** 713–719.
2. Gupta AK, Arshad S, Poulter NR. *Hypertension* 2010; **55:**399–407.
3. Juday T *et al. AIDS Care* 2011; **23:** 1154–1162.

Fixed dose combinations (FDC): 1

- Lower virological response if baseline VL >100 000 for RPV-based regimens when dosed as separate agents in ECHO/THRIVE1, not repeated as FDCs in STaR2:
  - May also be due to simpler regimens, other study differences or chance
- FDCs prevent patients adhering less closely to one component of a regimen; 'differential' adherence reported by a minority in one study but no impact on outcomes3
- Atripla switch to multi-tablets did not result in increased virological failures on one low quality study4 but insufficient evidence to support this strategy at present
- "FDCs support adherence which may reduce risk of virological failure. However, the size of this effect is yet to be defined"

1. Cohen CJ *et al. AIDS* 2012 Dec 3.
2. Cohen C *et al. 11th International Congress on Drug Therapy in HIV Infection.* Glasgow, Scotland. November 2012 [Abstract Oral 425].
3. Gardner EM *et al. AIDS* 2008; **22:** 75–82; 41. 4. Engsig F, Gerstoft J, Helleberg M *et al. CROI.* Atlanta, GA. March 2013 [Abstract Poster 5

What to start 2012: hepatitis B

- We recommend patients with HIV and hepatitis B virus co-infection who start ART include tenofovir and emtricitabine as part of their ART regimen, if there are no contraindications for either drug

What to start 2013: hepatitis B

- We recommend TDF/FTC as part of a fully suppressive ART combination
- We recommend neither 3TC nor FTC be used as the sole active drug against HBV in ART due to rapid emergence of HBV resistance
- We recommend 3TC/FTC may be omitted from the ART regimen and tenofovir given as the sole anti-HBV active agent if clinical or genotypic evidence of 3TC/FTC-resistant HBV or HIV

What 2013: HCV/HIV coinfection

SITUATION	RECOMMENDATION
DAA not planned	**Recommend** commence standard 1st line ART
DAA planned	**Recommend** careful consideration of possible DDI and current/archived HIV resistance. Check all DDI with an expert source (eg Liverpool)
Boceprevir	**Recommend** RAL with TDF/FTC if wild type HIV; PK data support ETV, RPV & MVC alternatives
Telaprevir	**Recommend** RAL or standard dose ATV/r should be used; PK supports ETV, RPV, MVC as alternatives. EFV may be used (with TPV dose increased to 1125mg TDS)
Abacavir with ribavirin	**Suggest** ribavirin should be weight-based dose-adjusted

Patient involvement in decision making

Pre-treatment

- Before prescribing ART (initiation/switching) assess:
  - Patients' readiness to take therapy
  - Knowledge of mode of action and efficacy, and perceptions of their personal need for ART
  - Concerns about taking ART or specific ARV drugs including potential adverse effects.
  - Concerns with possible adverse social consequences, such as disclosure or interference with lifestyle
  - Their confidence they'll be able to adhere (self-efficacy)
  - Psychological or NC issues that could impact on adherence
  - Socio-economic factors that could impact on adherence

Patient involvement in decision-making

- **Recommendations:**
  - We recommend patients are given the opportunity to be involved in making decisions about their treatment [GPP]
  - Provision of treatment-support resources should include in-house, independent and community information providers and peer-support resources
- *"A 'perceptions and practicalities' approach should be used to tailor support to meet the needs of the individual, to identify both the perceptual factors (such as beliefs about ART) and practical factors (such as capacity and resources) influencing adherence"*

Novel strategies

PI monotherapy

- We recommend against the use of protease inhibitor monotherapy as **initial therapy** for treatment-naïve patients [1C]
- We recommend against the use of PI-based dual ART with a single NRTI, NNRTI, C–C chemokine receptor type 5 (CCR5) receptor antagonist or INI as initial therapy for treatment-naïve patients [1C]

However as with other novel strategies there may be specific circumstances where a rationale for its use may be made.

PI monotherapy

- We recommend continuing standard combination ART as the **maintenance strategy** in virologically suppressed patients. There are insufficient data to recommend PI/r monotherapy in this clinical situation [1C]

No significant clinical benefit of PI monotherapy vs standard cART, which might offset the disadvantage of a lower rate of viral suppression with PI monotherapy. For this reason PI monotherapy should not be used in <u>unselected</u> patient populations

Special populations

HIV associated neurocognitive impairment

- Start ART (any CD_4) if symptomatic HIV-associated neurocognitive disorders
- Suggest avoidance of PI monotherapy in neurologically symptomatic patients
- Ongoing or worsening NC impairment despite ART (Best practise)
  - re-assessment for confounding conditions
  - assessment of CSF HIV RNA with genotyping
  - modifications to ART should be based on plasma and CSF genotypic results

Renal

- Start ART if HIVAN or end-stage kidney disease and candidate for transplant irrespective of CD4 [1C]
- We recommend against the use of antiretroviral drugs that are potentially nephrotoxic, in patients with stages 3–5 CKD if acceptable alternative antiretroviral agents are available [GPP]
- We recommend dose adjustment of renally cleared antiretroviral drugs in patients with reduced renal function [GPP] *but caution against the risk of over-interpreting estimates of renal function for this purpose as true measures of renal function may be substantially higher in patients with mild to moderate renal impairment*

Drug-specific advice

- *"The nephrotoxic potential of both TDF and ATV is low in patients with normal renal function. However, in patients with CKD and impaired renal function (eGFR <75 mL/min/ 1.73m2), alternative ARVs should be considered"*
- *"NNRTIs, INIs, ABC and 3TC have not been associated with CKD and can be used in HIV-positive patients with CKD"*

Cardiovascular disease

- **When**
  - There are insufficient data to inform whether CVD risk should affect decision to start ART (was a reason fro earlier ART in 2008 guidelines but not 2012/2013)
- **What**
  - We suggest avoiding ABC, FPV/r and LPV/r in patients with a high CVD risk, if acceptable alternatives available [2C]
- **Maraviroc caution:**
  - Coronary artery disease reported in MVC arm of MOTIVATE (experienced), no signal in MERIT (naïve)
  - Special caution in MVC use in patients with a high CVD risk

Other recommendations

Interventions to increase adherence to treatment

- We recommend adherence and potential barriers to it are assessed and discussed with the patient whenever ART is 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) to adherence [GPP]

Pharmacology

- We recommend potential adverse pharmacokinetic interactions between ARV drugs and other concomitant medications are checked before administration (with tools such as http://www.hiv-druginteractions.org) [GPP]
- We recommend against the unselected use of therapeutic drug monitoring (TDM) [GPP]
- We recommend patients stopping ART containing an NNRTI in combination with an NRTI backbone replace all drugs with a PI (LPV/r) for 4 weeks. [1C]
- We recommend patients stopping a PI-containing regimen stop all drugs simultaneously; no replacement required [GPP]

Switching/stopping antiretrovirals in combination ART

- We recommend in patients on suppressive ART regimens, consideration is given to differences in side effect profile, drug–drug interaction (DDIs) and drug resistance patterns before switching any ARV component. [GPP]
- We recommend, in patients with previous NRTI resistance mutations, against switching a PI/r to either an NNRTI or an INI as the third agent [1B]
- We recommend against treatment interruption or intermittent therapy in patients stable on a virally suppressive ART regimen [1A]

Switching from efavirenz

- Concerns re enzyme induction
- No good studies to guide clinical practice
- Early toxicity switch when still detectable VL
  - Switch to bPI recommended
- Switch when VL<50
  - Nevirapine:
    - packet insert recommends dose escalation. BHIVA also states that full dose has been shown to be OK
  - bPI/raltegravir/other NNRTIs:
    - Straightforward switch

Blips and low-level viraemia

- Blips not a cause for concern
- LLV (repeatedly detectable VL<400)
  - Associated with virological failure
  - *In the absence of clear data, the committee believes LLV on a low genetic barrier regimen warrants prompt regimen change. This is especially true where ART combination without a boosted PI is being used*

Managing virological failure

- Several recommendations grouped by presence/degree of resistance including:
  - We recommend patients experiencing virological failure on first-line ART with wild-type virus at baseline and without emergent resistance mutations at failure switch to a PI/r-based combination ART regimen [1C]
  - We recommend against switching a PI/r to an INI or an NNRTI as the third agent in patients with historical or existing reverse transcriptase (RT) mutations associated with NRTI resistance or past virological failure on NRTIs [1B]

Specific populations

- Tuberculosis
- HIV-related cancers
- HIV-associated neurocognitive impairment
- Chronic kidney disease
- Women