

BHIVA antiretroviral treatment guidelines 2015

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†Professor Martin Fisher died in April 2015 – he made a significant contribution to these, many other guidelines and our speciality as a whole – he is greatly missed.

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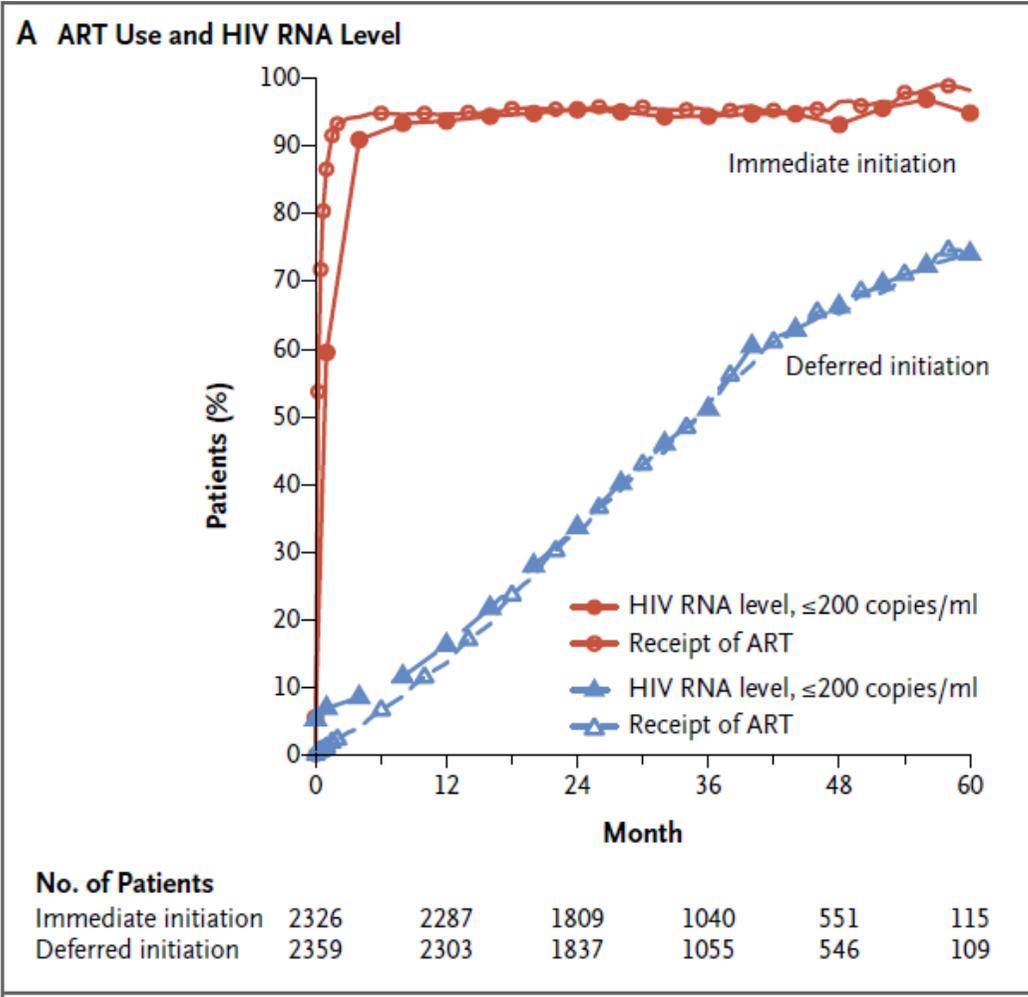
GENERAL POINTS & WHEN TO START

When to start 2012/2013

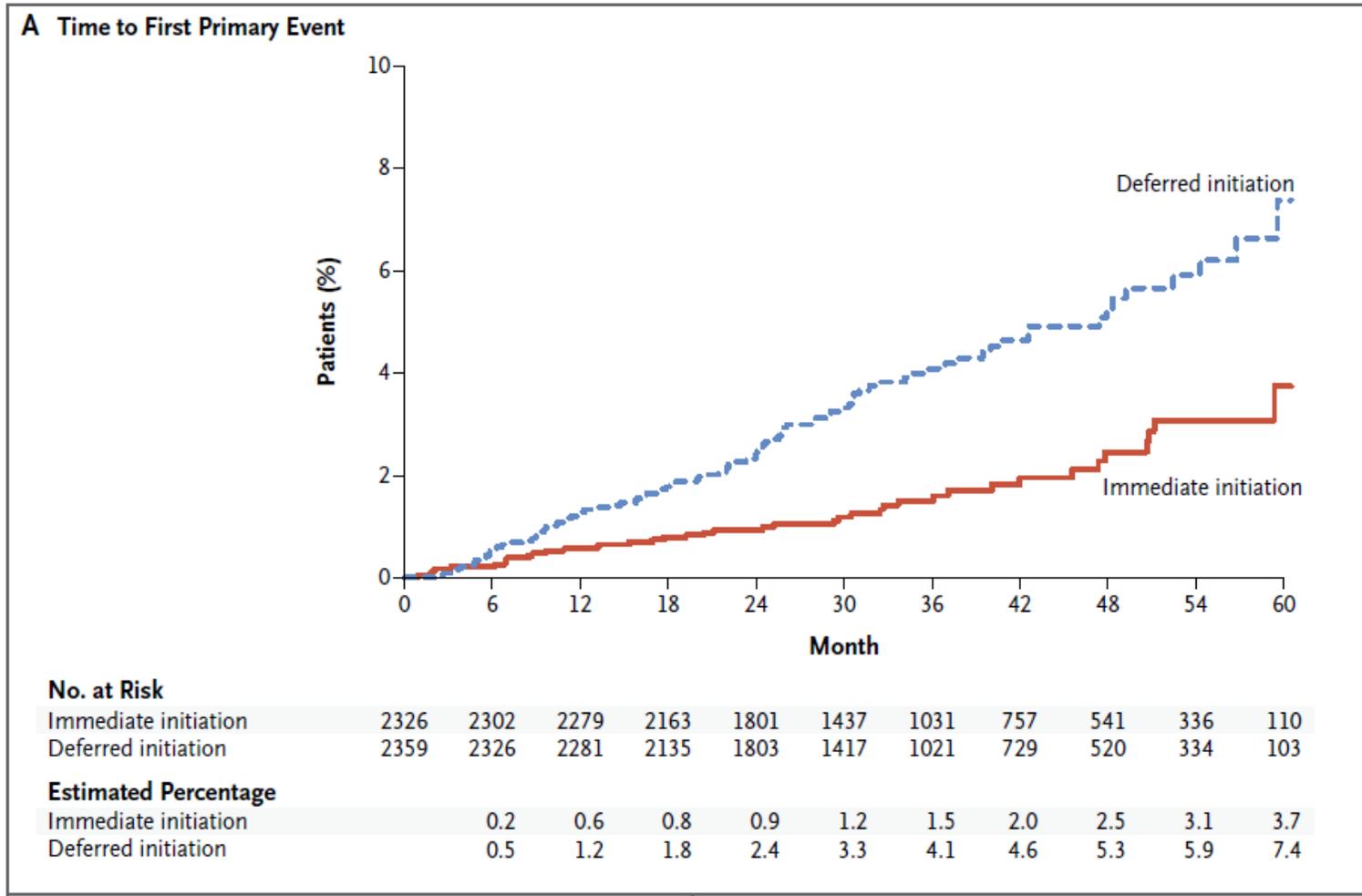
We recommend starting ART in patients:

- Before CD4 <350 [1A] (Consider earlier if older)
- Or with the following conditions:
 - AIDS [1A]
 - HIV-related co-morbidity [1C]
 - HBV [1B]
 - HCV [1C] if the CD4 count is ≤ 500
 - nADM requiring immunosuppressive radiotherapy or chemotherapy [1C]
- Or to reduce the risk of transmission of HIV to others

START



START



4.1 Chronic infection

4.1.1 Recommendations

- We recommend people with HIV start ART (1A).



Public Health
England

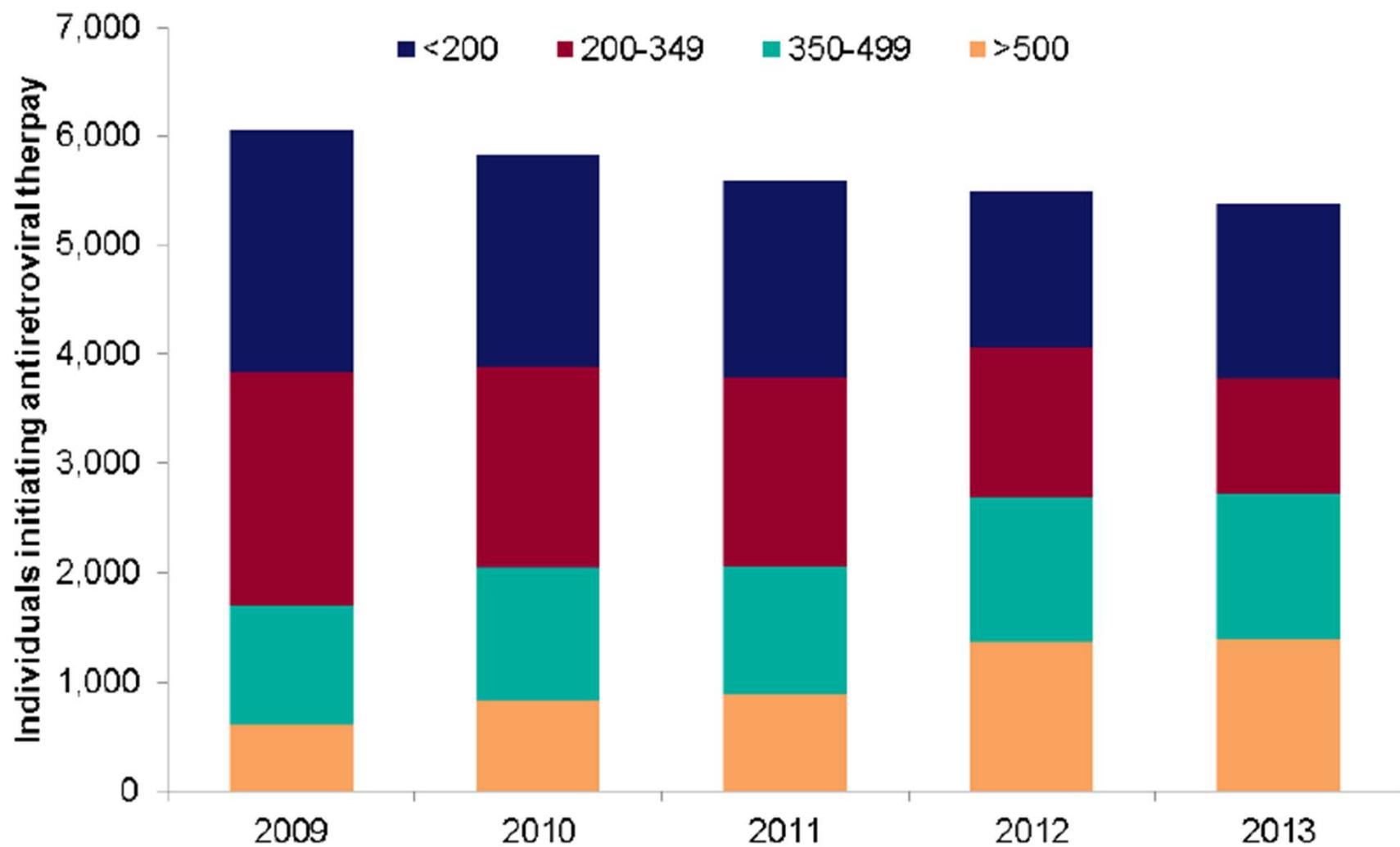
Protecting and improving the nation's health

HIV New Diagnoses, Treatment and Care in the UK 2015 report

2014

- 85,489 people seen for care in UK
 - 91% on ART
 - 95% of these have undetectable viral load
- Around 7,700 people with diagnosed HIV who are not on ART

Figure 4: Number¹ of adults starting ART by CD4 count at initiation²; UK 2009-13



¹ Adjusted for CD4 count not reported.

² CD4 count available up to 9 months before ART initiation

BHIVA

“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. In this study, 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.”

WHO

2.1 When to start antiretroviral therapy

2.1.1 When to start ART among adults (>19 years old)

NEW

Recommendation

- ART should be initiated among all adults with HIV regardless of WHO clinical stage and at any CD4 cell count (*strong recommendation, moderate-quality evidence*).
 - As a priority, ART should be initiated among all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count ≤ 350 cells/mm³ (*strong recommendation, moderate-quality evidence*).

DHHS

With the availability of the START and TEMPRANO trial results, the Panel's overall recommendation remains the same: ART is recommended for all HIV-infected patients regardless of pre-treatment CD4 count. However, the strength of the recommendation will be changed to AI^a (strong recommendation based on data from randomized controlled trials) for all patients.

The additional benefit of ART in reducing the risk of HIV transmission further underscores the potential public health value of this recommendation. The Panel continues to emphasize that patients starting ART should be willing and able to commit to treatment and to understand the benefits and risks of therapy and the importance of adherence. On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors, but therapy should be initiated as soon as is feasible.

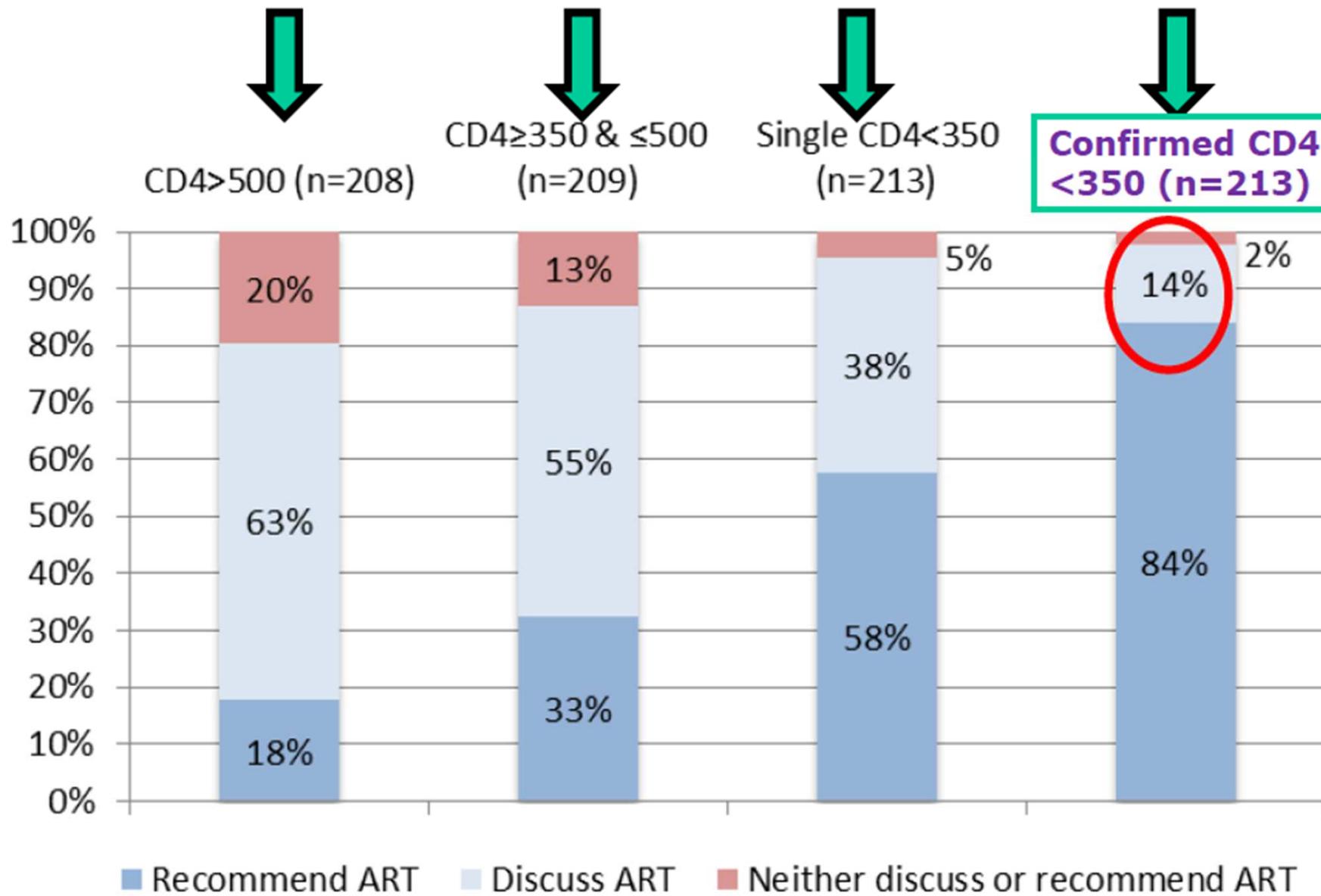
Primary Infection

Primary infection

ART should be started only when the individual feels ready to do so. However, there are certain clinical presentations of PHI where expedited ART initiation should be recommended. We recommend starting ART as soon as possible for patients presenting with PHI meeting any one of the following criteria known to be associated with morbidity or very rapid disease progression:

- Neurological involvement (1D)
- Any AIDS-defining illness (1A)
- CD4 cell count <350 cells/ μ L (1C)
- PHI diagnosed within 12 weeks of a previous negative test (1C)

Asymptomatic PHI, Regular HIV +ve partner



When to start 2015

- Various specific situations when ART relatively 'urgent'
 - Primary HIV
 - HIVAN, malignancies
 - HCV/HBV coinfection
 - Treatment as prevention

Cost-effectiveness & commissioning

- Immediate ART unlikely to meet cost-effectiveness thresholds in UK

NHSE: early treatment

NHS England does not currently routinely commission early treatment initiation in HIV. The published service specification notes that treatment can be initiated at CD4 350 or below unless patients have a defined comorbidity. NHS England has however published a 'Treatment as Prevention' policy in 2015 which allows for earlier treatment where the sexual partners of diagnosed patients are at risk of infection. Local commissioning hubs will be validating treatment initiation and requiring Trust assurance that processes are in place to evidence that treatment initiation is in line with the service specification. The CRG has identified this as a workplan item for 16/17. This will be developed as a policy proposition for 17/18 unless it meets the criteria as an in year service development.

The British Isles



My personal view

- We need to resolve the commissioning of earlier treatment in-year

Laura Waters

WHAT TO START

Laura: Conflicts of interest

- Speaker fees, ad board fees or conference support from Gilead, ViiV, MSD, BMS, AbbVie & Janssen

What to start with: BHIVA 2012

	PREFERRED	ALTERNATIVE
NRTI	TDF & FTC	ABC & 3TC ^{1,3}
3 rd 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

What to start with: BHIVA 2013

	PREFERRED	ALTERNATIVE
NRTI	TDF & FTC	ABC & 3TC ^{1,3}
3 rd 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>400/250
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What to start with: BHIVA 2015

	PREFERRED	ALTERNATIVE
NRTI	TDF & FTC	ABC & 3TC ^{1,2}
3 rd agent	ATV/r DRV/r DTG EVG/COBI RAL RPV³	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

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

Changes to NRTI

- **Kivexa remains alternative**
 - The advice regarding use at VL >100,000 does not apply when Kivexa is combined with dolutegravir
- **FTC vs 3TC**
 - 7 RCTs comparing FTC and 3TC (2000-2015)
 - In only 2 this was the only variable
 - Both of these studies unpublished

It is clear that the evidence concerning this question is mixed and of variable quality, leaving open the question of whether lamivudine and emtricitabine are interchangeable in first-line therapy. The paucity of sufficiently high-quality evidence addressing this question means that tenofovir/lamivudine cannot be clearly recommended as an alternative nucleoside backbone when initiating first-line therapy.

If cost pressures become such that co-formulation is no longer a major driving factor in antiretroviral choice, then it will be reasonable to revisit this recommendation.

Changes to 3rd agent

- Three agents **removed**
 - **Lopinavir/r**: inferior to other 3rd agents in RCT, ?renal, ?CV
 - **Fosamprenavir/r**
 - **Nevirapine**: remains an excellent choice if already on it but the small risk of significant toxicity no longer acceptable in era of well-tolerated alternatives
- One agent **added**
 - **Dolutegravir**: superior to two 3rd agents, non-inferior to raltegravir, no resistance in first-line use

Changes to 3rd agent

- One agent **upgraded**
 - **Rilpivirine:** based on decision to consider this agent within its license (ie at VL <100,000)
- One agent **downgraded**
 - **Efavirenz:**
 - inferior to dolutegravir (SINGLE, primary endpoint), raltegravir with enough follow-up (STARTMRK), rilpivirine in <100k subgroup (STaR)
 - Lipids
 - ACTG suicidality analysis

(no) Changes to 3rd agent

- Four agents **stay**
 - Raltegravir
 - Elvitegravir/c
 - Darunavir/r
 - Atazanavir/r

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 & VL <100,000 where there is a need to avoid abacavir or and 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)

Special populations

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

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)	<ul style="list-style-type: none"> • 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 	<p>No dose adjustment is required for darunavir/ritonavir in patients with renal impairment</p> <p>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 creatinine clearance <70 ml/min if any co-administered agent requires dose adjustment based on creatinine clearance: e.g. emtricitabine, lamivudine, tenofovir.</p> <p>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.</p>	<p>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</p> <p>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.</p>
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 for Antiretrovirals

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

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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	<p>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.</p> <p>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 C_{max} by 46%, 52%, and 67%, prolonged T_{max} 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.</p>
 Elvitegravir Vitekta [®] (EVG)	85 mg or 150 mg once daily depending on coadministered ritonavir-boosted PI	<p>Must be taken with food Relative to fasting conditions, administration of elvitegravir as the fixed-dose combination (Stribild[®]) with food increased EVG C_{max} 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.</p>
 Maraviroc Celsentri [®] (MVC)	150 mg, 300 mg or 600 mg twice daily, depending on interactions with co-administered medicinal products	<p>Can be taken with OR without food Administration with a high fat breakfast reduced maraviroc C_{max} 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</p>
 Raltegravir Isentress [®] (RAL)	400 mg administered twice daily	<p>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 C_{12 hr} was 66% higher and C_{max} was 5% higher following a moderate-fat meal compared to fasting. Administration following a high-fat meal increased AUC and C_{max} ~2-fold and increased C_{12 hr} 4.1-fold. Administration following a low-fat meal decreased AUC and C_{max} by 46% and 52%, respectively. Food appears to increase pharmacokinetic variability relative to fasting.</p>

Cost-effectiveness

- Increasingly clear that new agents will require cost-effectiveness evidence for approval
- BHIVA in discussion with
 - CRG
 - NICE
- Lack of uniform price makes this more complex
- **How can national guidelines perform cost-effectiveness analyses based on REGIONALLY VARIABLE, RAPIDLY CHANGEABLE, BEHIND CLOSED DOOR prices?**

NHSE: initial therapy

NHS England does not currently commission the BHIVA ART treatment guidelines 2015.

Local commissioning hubs will be validating drug usage to ensure Trusts continue to focus on use of the lowest cost clinically effective treatments options and avoid switches which increase costs without demonstrated improvements in outcomes. Where regional drug volume/price frameworks and guidelines are in place these continue to guide prescribing decisions.

The CRG has identified this as a workplan item for 16/17 and it is intended to develop a general HIV treatment policy proposition for 17/18 unless it meets the criteria as an in year service development.

The British Isles



My personal view?

- Increased use of generics
- Stronger guidance to use cheaper options first-line with a low threshold for switching for intolerance
- We need a standardised approach to assessing mood before and during efavirenz treatment
- We need to decide if we are happy to use raltegravir OD
- Individualisation remains crucial

Acknowledgements

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- Andy Winter

Thank you!



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