

# London Therapeutic Tender Implementation: Guidance for Clinical Use

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# General principles

- The tendering process has realised large savings for the NHS.
- Good medicines management remains a cornerstone of cost-effective HIV treatment.
- This guidance strives to achieve best value whilst maintaining access to alternative regimens which may be more tolerable for some patients.
- Current BHIVA guidelines [1] and data from recent conferences/publications has been considered when making decisions (excepting for the caveats for Kivexa use on slide 10).
- Good communication between clinicians, commissioners and people living with HIV is essential in making effective treatment decisions.
- We recommend patients are given the opportunity to be involved in making decisions about their treatment [1].
- Informed patient choice should be central to all treatment decisions.

# Financial impact of Therapeutic Tendering for branded ARVs

- Annual expenditure on ARVs in London is currently **£190m**.
- Since 2011, Therapeutic Tendering saved at least **£10.5m** (recurring full year savings).
- This is equivalent to a reduction of about **5.2%** in annual ARV expenditure.
- The new therapeutic contract starting in April 2014 is expected to save at least **£4.8m (2.5%)**.

# London ARV algorithm: First line therapy

Patient requires ARV therapy for the first time:  
Commence Kivexa + efavirenz where clinically appropriate

Efavirenz not suitable [1, 3]

Kivexa not suitable [2, 3]

HIV resistance [4]?

HIV resistance?

No resistance:  
Alternative first line options:  
2 NRTI + raltegravir

Yes, refer to virtual clinic [3] and consider:  
Atazanavir/ritonavir or darunavir/  
ritonavir based ART

If raltegravir not suitable, refer to virtual clinic [3] and consider:  
2 NRTI + atazanavir/ritonavir  
2 NRTI + darunavir/ritonavir  
2 NRTI + dolutegravir [5, 6]  
Eviplera [7]  
Stribild [5]

If no resistance, alternative first line backbone option if appropriate:  
Truvada

See NEXT slide for key

# London ARV algorithm: First line therapy - Key<sup>6</sup>

1. Caution with **efavirenz** where evidence of clinical depression or other significant mental health issues, or where side effects of **efavirenz** are likely to have an impact on the shift work or lifestyle of patients, impacting on adherence.
2. **Kivexa** not indicated if: HLA-B\*5701 positive, baseline VL is >100,000 c/ml (unless with dolutegravir), HBV co-infection, resistance to **abacavir** or **lamivudine**, or patients with higher cardiovascular risk (>10% ten-year risk). See BHIVA treatment guidelines (2014) for definition and assessment. (Churchill D et al. HIV Medicine (2014), 15 (Suppl. 1), 1–85).
3. Virtual clinic (multi-disciplinary team meeting) referral should be made for all patients who do not fulfil the outlined clinical criteria for exceptions to use of **Kivexa**, or who require third agents other than **efavirenz** or **raltegravir**, or those with HIV antiretroviral resistance or where **dolutegravir**, **Triumeq** or **Stribild** or is being considered (see point 5). If there is a clinical need to initiate a non-preferred regimen then local mechanisms should be established to review retrospectively.
4. If urgent treatment is required prior to availability of baseline resistance assay then start PI/r based ART and review in line with guidance when resistance assay available.
5. Prescribed In line with NHS England Clinical Commissioning Policy Statements for **Stribild** (September 2013 Reference NHS England B06/PS/a) and **dolutegravir** and **Triumeq** (January 2015 NHS England B06/P/a).
6. **Kivexa + dolutegravir 50mg OD** should be used in preference to **Triumeq**.
7. **Eviplera (or rilpivirine)** is not indicated where HIV viral load is >100,000 c/mL.

# Key points (1)

- First line therapy
  - **Kivexa** remains the NRTI backbone of choice where clinically appropriate for patients starting ART.
  - **Efavirenz** is the preferred third agent unless there is a clinical contra-indication.
- Patients currently on stable therapy
  - London guidance does not recommend switching treatment for patients who are on stable treatment unless there is a clinical reason.

## Key points (2)

- If there is a clinical indication to avoid, or to switch because of **efavirenz** toxicity:
  - Consider use of **raltegravir**.
- If there are potential adherence concerns with twice daily **raltegravir**:
  - Consider 2NRTIs (preferably **Kivexa**) with **atazanavir/r**, **darunavir/r**, **dolutegravir [1]**, **Eviplera** or **Stribild** with review by virtual clinic.
  - In patients with baseline drug resistance or concerns regarding intermittent adherence use boosted **atazanavir** or **darunavir**.

1. Dolutegravir / Triumeq should be used in line with NHS England. Clinical Commissioning Policy Statement: Dolutegravir January 2015 NHS England B06/P/a.



## Key points (3)

- Referral to multi-disciplinary team meetings (virtual review and audit clinic) should be made for all patients who:
  - Do not fulfil the outlined clinical criteria for exceptions to use of **Kivexa**, or require regimens that do not contain **efavirenz** or **raltegravir**.
  - Whenever **atazanavir**, **darunavir**, **dolutegravir**, **Eviplera**, **Stribild** or **Triumeq** are being considered.
- PI monotherapy is not a recommended strategy.

# Choice of NRTI backbone

- The London HIV Drugs & Treatment Group has seen no new data to support changing London recommendations made in 2012 on choice of **Kivexa** vs **Truvada**.
- Following the 2012 guidance, cost must be taken into consideration when choosing the NRTI backbone.
- Where clinically appropriate, **Kivexa** remains the NRTI backbone of choice.
- **Truvada** should be considered where:
  - Baseline HIV viral load is above 100,000 copies/mL, unless there are other clinical considerations (e.g. renal impairment). Note: if **dolutegravir** is indicated **Kivexa** should be used as the NRTI backbone regardless of VL.
  - Co-infection with Hepatitis B.
  - In patients at higher cardiovascular risk (>10% ten-year risk) - see BHIVA treatment guidelines (2014) for definition and assessment. [1]
  - Where patient is HLA-B\*5701 positive (**Kivexa** contraindicated).

# Choice of 3<sup>rd</sup> agent

- **Efavirenz** is the preferred third drug for first line therapy.
- If efavirenz is not clinically appropriate, **raltegravir** is the recommended alternative.
- In patients with baseline drug resistance or concerns regarding intermittent adherence, ritonavir boosted **atazanavir** or **darunavir** should be used.
- If there are concerns over adherence to twice daily therapy, then **atazanavir/r** or **darunavir/r** or **dolutegravir** (preferably with **Kivexa**), **Eviplera** or **Stribild** should be considered.

# Exceptions to efavirenz use

- No change to 2012 guidance [1], other than BHIVA pregnancy guidelines now allow the use of **efavirenz**. However, some clinicians and patients will still prefer to use other third drugs.
- It is recommended that clinicians avoid efavirenz in patients with clinical depression or other significant mental health issues or where side effects of **efavirenz** may have an impact on the work or lifestyle of patients, impacting on adherence.

1. London DTSG 2011 guidance: Efavirenz not suitable if: Patient has baseline resistance, patient wants to become pregnant, concern over central nervous system (CNS) side effects e.g. previous history or current psychological state

# Raltegravir

- When **efavirenz** is unsuitable then **raltegravir** is the recommended alternative, except in patients with baseline resistance.
- **Raltegravir** may be advantageous in those with co-morbidities due to:
  - Relatively few drug-drug interactions [1] compared to PI/r.
  - A good side effect profile compared to PI/r.
  - Less impact on lipids.

1. Caution with patients using supplements/antacids/multivitamins containing divalent or trivalent cations (e.g. Mg/Al/Ca/Zn/Fe) which may chelate raltegravir, dolutegravir or elvitegravir. Consult SPCs for raltegravir and all integrase inhibitors for advice.

# Dolutegravir vs. raltegravir

- Although once-daily combinations are preferred for adherence, many patients would choose twice daily if it had fewer side effects or drug interactions.
- The new lower price for twice-daily **raltegravir** means this can now be used as an alternative to **efavirenz**, and in preference to other options.
- Because of its higher price, **dolutegravir** can only be used as a once-daily alternative to **raltegravir** after referral to the virtual clinic.

# Fixed dose combinations (FDC)

- There is no additional evidence of improved virological success for FDCs compared with separate components.
- FDCs should not be prescribed in preference to other appropriate regimens within the guidance.

# Boosted protease inhibitor choice

- A boosted protease inhibitor (PI/r) is recommended as first-line therapy in the following situations:
  - Primary drug resistance.
  - Where intermittent adherence seems likely and there is concern about the development of drug resistance.
  - If there are concerns over twice-daily therapy, a **boosted-PI** (preferably with **Kivexa**) can be considered. The recommended PIs are **ritonavir boosted atazanavir** or **darunavir**.
  - If treatment is required prior to availability of baseline resistance assay then start PI/r based ART and review in line with guidance when resistance assay available (or refer to virtual clinic for review).
- Clinicians should consider drug-drug interactions and the resistance and side effect profile in choosing between PIs, and other available third drugs.



# Stribild (TDF/FTC/c/EVG)

- **Stribild** should be considered as an alternative option in patients not suitable for **efavirenz** or **raltegravir**, with review by the virtual clinic.
- **Stribild** contains **cobicistat** which is associated with frequent drug interactions, some of which may be similar to those seen with ritonavir.
- For patients switching therapy **Stribild** may be considered for patients without resistance, in whom **raltegravir** is not suitable after review by the virtual clinic.
- **Stribild** should be used in accordance with the NHS England clinical commissioning policy statement. [1]

1. NHS England. Clinical Commissioning Policy Statement: Stribild for the treatment of HIV-1 infection in adults: September 2013 Reference NHS England B06/PS/a

# Eviplera (TDF/FTC/RPV)

- **Eviplera** should only be considered as an alternative option in patients not suitable for **efavirenz** or **raltegravir**, with review by the virtual clinic.
- For patients switching therapy **Eviplera** may be considered for patients without resistance, in whom **raltegravir** is not suitable after review by the virtual clinic.

# Switching therapy

- If switching for **efavirenz** toxicity (in absence of viral failure or resistance) the recommended switch option is **raltegravir**.
- If **raltegravir** is not indicated, then **atazanavir/r**, **darunavir/r**, **dolutegravir**, **Eviplera** or **Stribild** should be considered.
- Patients stable on **atazanavir/r** or **darunavir/r** should not be switched between PIs unless there are clear clinical indications to do so, and these should preferably be discussed at the virtual clinic.

# Multi-disciplinary review (virtual clinic)

- The use of virtual clinics (VCs) to review patients starting or switching therapy is good clinical practice.
  - Patients needing to initiate or switch to a non-preferred regimen [1] should be discussed in a VC as per best practice.
  - Where there is urgent need to use a non-preferred regimen, local mechanisms to discuss retrospectively in the VC should be developed.
1. Non preferred regimens include plan to use regimens other than Kivexa with efavirenz or any first-line regimen not containing efavirenz or raltegravir where the indication for the alternative regimen is not within the guidance (i.e. initiating Atripla with HIV VL is >100,000 copies/mL or HBV co-infection, or use of raltegravir due to clinical depression would not require referral to the virtual clinic). Switching therapy to non-raltegravir or non-efavirenz containing regimens (with two NRTIs) should be reviewed by the virtual clinic.

# Audit / review of Guidance

- A 6 month prospective audit of all patients starting ART started in December 2014.
- An audit of those switching within six months is planned.
- Centres using higher proportions of non-efavirenz based regimens will have external audit of their virtual review and audit clinic.

# Protease Inhibitor monotherapy

- The London group does not recommend PI monotherapy other than in specific clinical situations such as the need to avoid NRTI toxicity with limited options.
- If PI monotherapy is used then **darunavir/r** is the recommended PI.
- **Atazanavir** is not recommended as PI monotherapy.

# Dolutegravir

- **Dolutegravir** should be used in accordance with the NHS England clinical commissioning policy statement [1], including need for review at the virtual clinic.
- **Dolutegravir + 2 NRTIs** should be considered as one of the alternative options (see algorithm) in treatment naive patients not suitable for **efavirenz** or **raltegravir**.
- For patients switching therapy **dolutegravir + 2NRTIs** may be considered for patients without resistance, in whom **raltegravir** is not suitable.

1. NHS England. Clinical Commissioning Policy: Dolutegravir for the treatment of HIV-1 infection in adults and adolescents: January 2015 Reference NHS England B06/P/a.

# Dolutegravir / Triumeq

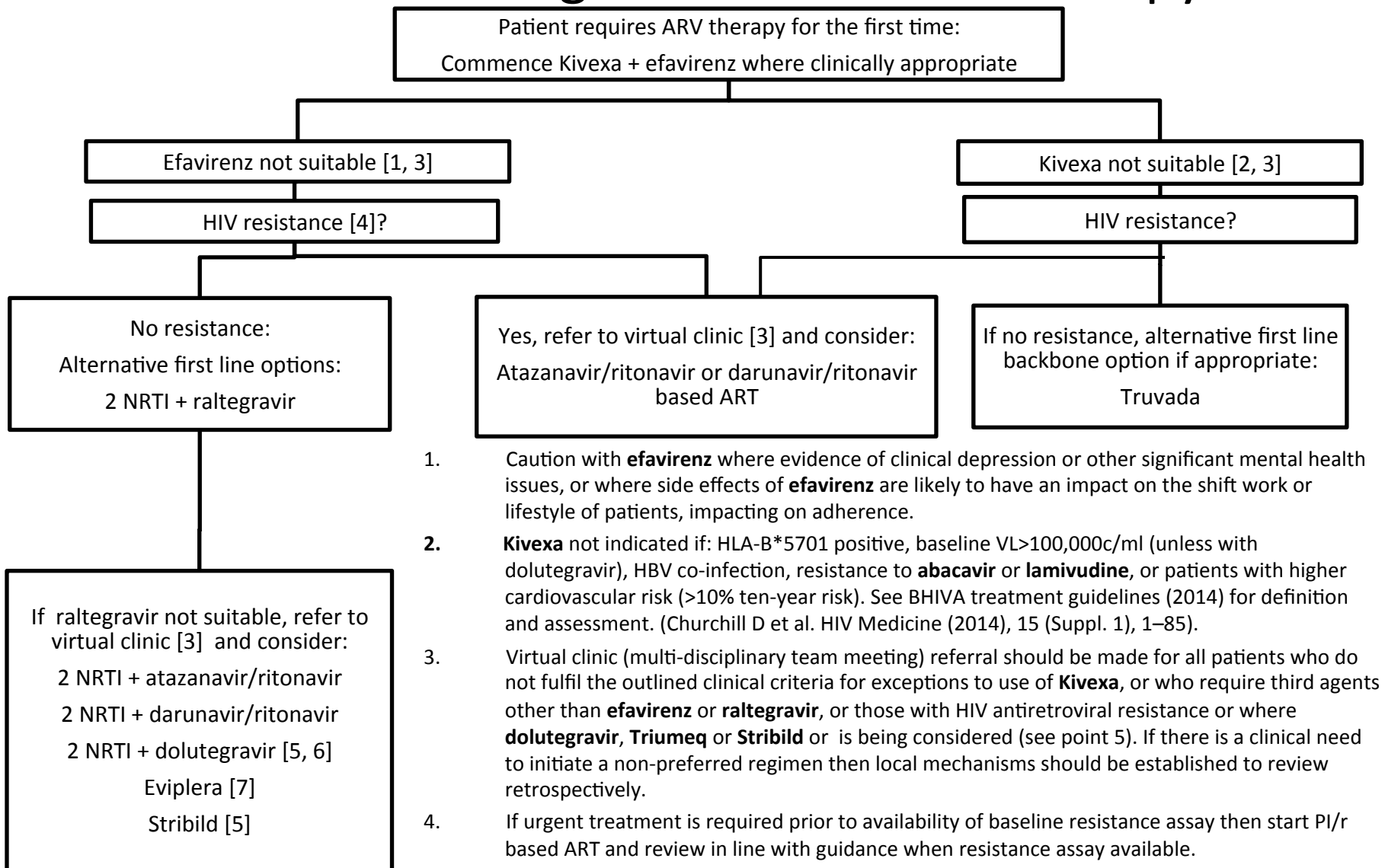
- **Dolutegravir** should be used in combination with **abacavir/lamivudine** unless:
  - Co-infection with Hepatitis B.
  - In patients at higher cardiovascular risk (>10% ten-year risk)
    - see BHIVA treatment guidelines (2014) for definition and assessment. [1]
  - The patient is HLA-B\*5701 positive (**Kivexa** contraindicated).
  - Baseline NRTI resistance
- **Kivexa + dolutegravir 50mg OD** should be used in preference to **Triumeq**.
- If there are exceptional circumstances where **Triumeq** is indicated then it may be considered with virtual clinic review.



# Prescribing of generic ARVs

- Where there are contracts for generic ARVs, patients should be switched from the branded equivalent as soon as possible, taking into account the need for the provision of appropriate information and counselling.

# London ARV algorithm: First line therapy



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2. **Kivexa** not indicated if: HLA-B\*5701 positive, baseline VL>100,000c/ml (unless with dolutegravir), HBV co-infection, resistance to **abacavir** or **lamivudine**, or patients with higher cardiovascular risk (>10% ten-year risk). See BHIVA treatment guidelines (2014) for definition and assessment. (Churchill D et al. HIV Medicine (2014), 15 (Suppl. 1), 1–85).
3. Virtual clinic (multi-disciplinary team meeting) referral should be made for all patients who do not fulfil the outlined clinical criteria for exceptions to use of **Kivexa**, or who require third agents other than **efavirenz** or **raltegravir**, or those with HIV antiretroviral resistance or where **dolutegravir**, **Triumeq** or **Stribild** or is being considered (see point 5). If there is a clinical need to initiate a non-preferred regimen then local mechanisms should be established to review retrospectively.
4. If urgent treatment is required prior to availability of baseline resistance assay then start PI/r based ART and review in line with guidance when resistance assay available.
5. In line with NHS England. Clinical Commissioning Policy Statements for **Stribild** (September 2013 Reference NHS England B06/PS/a) and **dolutegravir and Triumeq** (NHS England B06/P/a).
6. **Kivexa + dolutegravir 50mg OD** should be used in preference to **Triumeq**.
7. **Eviplera or rilpivirine** is not indicated where HIV VL>100,000c/ml.