Advanced HIV Disease (AHD) CME

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TREATMENT OPTIMISATION
Treatment Optimisation

• The new HIV treatment guidelines include new alternative ARV options
  – Better tolerability
  – Higher efficacy
  – Lower treatment discontinuation
• Transition to dolutegravir has already started in 82 low- and middle-income countries.
• Expected to improve the durability of treatment & quality of care for people living with HIV.
• 1 in 3 PLHIV present to care with advanced disease
  – Low CD4+ counts
  – At high risk of serious illness & death
• Globally 23.3 million PLHIV receiving ART in 2018
• Global ART coverage stands at a rate of 62%
• More efforts needed to scale up treatment
  – Particularly for children & adolescents
  – Only 54% of children & adolescents receiving ART in 2018
• Expanding access to treatment is at heart of a set of targets for 2020- by WHO
  – Aim is to bring the World back on track to end AIDS epidemic by 2030
• Number of new HIV infections globally in 2018 1.7 million
  – 1.1 million in Africa
Number of people newly infected with HIV

2000: 2.8 million
2018: 1.7 million
2020: Target < 500,000
2030: Target < 200,000

Source: UNAIDS/WHO estimates
Number of HIV-related deaths

- **2000**: 1.4 million
- **2018**: 770,000
- **2020**: < 500,000 (Target)
- **2030**: < 400,000 (Target)

Source: UNAIDS/WHO estimates
Number of people receiving antiretroviral treatment

Source: UNAIDS/WHO estimates

Future targets:
- 2020: 30 million
- 2030: 33 million
HIV testing and care continuum (2018)

- People living with HIV: 38 million
- Aware of HIV status: 30 million (79%)
- On treatment: 22 million (62%)
- Viral load suppression: 19 million (90%)

Source: UNAIDS/WHO estimates
South Africa

New HIV infections (all ages)

Source: UNAIDS Estimates 2019
South Africa

People living with HIV (all ages)

Source: UNAIDS Estimates 2019
South Africa

Progress towards 90-90-90 target

Source: UNAIDS special analysis, 2019
90-90-90 Cascade - Total Population
(Jun 2018 - South Africa)

Source: South Africa National Department of Health
Fig. 1 Temporal evolution of CD4 criteria to initiate ART in asymptomatic HIV+ adults (IAS, DHHS, EACS and WHO Guidelines). (1) Adapted from Marco Antonio Vitoria, WHO, Geneva. ART combined antiretroviral therapy. DHHS U.S. Department of Health and Human Services. EACS European AIDS Clinical Society. IAS International AIDS Society. WHO World Health Organisation.
Overview of Dolutegravir (DTG)
Goals of ART

- Decrease opportunistic infections and other HIV-related conditions
- Minimise the development of treatment resistance
- Decrease the morbidity and mortality from HIV/AIDS
- Improve quality of life

Achieve and maintain
Viral suppression

Minimise Rx side-effects and toxicity
Initial ART Regimens for the previously untreated patient

The preferred First-line regimens

- TDF + emtricitabine (FTC) (or 3TC) + efavirenz (EFV)
- TDF + emtricitabine (FTC) (or 3TC) + dolutegravir (DTG)
- TDF + emtricitabine (FTC) (or 3TC) + *rilpivirine (RPV) provided VL < 100,000 copies/mL

*Rilpivirine cannot be used with rifampicin & dolutegravir requires dose adjustment with rifampicin

Preferred 1st Line in Public sector up until 2019

Alternative 1st line regimen for private sector

1st line regimen for public & private sector 2020 & beyond
How ARVs Work

Some examples of integrase inhibitors are:
- Raltegravir (RAL)
- Elvitegravir (EVG)
- Cabotegravir (CAB)
- Bictegravir (BIC)
- Dolutegravir (DTG)
Integration

CD4 Cell

CD4 Cell Nucleus

Integrase

HIV DNA

CD4 Cell DNA

Integrase Inhibitors

CD4 Cell

CD4 Cell Nucleus

Integrase

HIV DNA

Integrate Inhibitor

Block insertion of HIV DNA into CD4 cell DNA

CD4 Cell DNA
# Safety and Efficacy of DTG versus EFV

<table>
<thead>
<tr>
<th>Major Outcomes</th>
<th>DTG Vs EFV</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral suppression</td>
<td>DTG better</td>
<td>Moderate</td>
</tr>
<tr>
<td>Treatment discontinuation</td>
<td>DTG better</td>
<td>High</td>
</tr>
<tr>
<td>CD4+ recovery</td>
<td>DTG better</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mortality</td>
<td>comparable</td>
<td>low</td>
</tr>
<tr>
<td>AIDS progression</td>
<td>comparable</td>
<td>low</td>
</tr>
<tr>
<td>SAE</td>
<td>comparable</td>
<td>low</td>
</tr>
</tbody>
</table>

Kanters S, For WHO ARV GDG, 16-18 May 2018
DTG: Dosages and Formulations

- **Class of ARV**: Integrase Inhibitor (InSTI)
- **Standard dose**: DTG 50mg daily
- **Who may get DTG?**
  - Children, adolescents and adults > 20kg
- **Formulations**:
  - **DTG 50mg tablet**
    - Children and adolescents 20 - 35kg
  - **Fixed-dose combination: TLD**
    - Tenofovir (TDF) 300mg + lamivudine (3TC) 300mg + DTG 50mg (TLD)
    - TLD can be prescribed for patients > 35kg and > 10 years of age (restricted by TDF)
- **DTG dose with concomitant TB Treatment**:
  - Double DTG dose to **50mg 12-hourly**
  - If on TLD FDC, add DTG 50mg 12 hours after TLD dose
8 Different TLD Manufacturers/Suppliers
Adverse Events Reported with DTG Use

- Nausea
- Diarrhea
- Sleep disorder (Insomnia)
- Headache
- Weight gain

Common AEs

DTG can be taken in the evening or the morning as per the client’s preference. However, if the client develops insomnia, TLD should be taken in the morning.
DTG Discontinuation in Clinical Practice

- 387 patients started DTG (65 naïve) (median CD4 650/mm³)
- 16% stopped after a median of 78 days (range 5-327), 20% of naïves

Reason

## Important drug-drug interactions with dolutegravir

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>Effect of co-administration</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>↑metformin</td>
<td>Maximum metformin dose 500 mg 12 hourly</td>
</tr>
<tr>
<td>Polyvalent cations (Mg, Fe, Ca, Al, Zn) e.g. antacids, sucralfate, supplements</td>
<td>↓dolutegravir</td>
<td>Take dolutegravir either 2 hours before or 6 hours after</td>
</tr>
<tr>
<td>Anticonvulsants: Carbamazepine</td>
<td>↓dolutegravir</td>
<td>Avoid co-administration if possible (lamotrigine, levetiracetam, and topiramate can be used) or double dolutegravir dose to 50 mg 12 hourly</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td></td>
<td></td>
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<tr>
<td>Phenytoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>↓dolutegravir</td>
<td>Avoid co-administration if possible (rifabutin 300 mg daily can be used) or double dolutegravir dose to 50 mg 12 hourly</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>↓dolutegravir</td>
<td>Avoid co-administration if possible (rilpivirine can be used) or double dolutegravir dose to 50 mg 12 hourly</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>↓dolutegravir</td>
<td>Avoid co-administration if possible (rilpivirine can be used) or double dolutegravir dose to 50 mg 12 hourly</td>
</tr>
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## Drug Interactions with DTG

### No interaction/or dose adjustment

- Hormonal contraceptives
- Anti-malarials
- Methadone
- Rifabutin
- Most antiarrhythmics
- Beta-blockers
- Anti-depressants

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https://www.hiv-druginteractions.org/checker
Pregnancy: Birth outcomes of 1st line DTG

• Tsepamo study- prospective cohort of HIV infected women in Botswana initiating ART with EFV/FTC/TDF vs DTG/FTC/TDF
  – data showed 0.67% of babies (4/596) to women on DTG when they conceived or early in the first trimester had neural tube defects (NTDs)
  – No NTDs observed in pregnancies where DTG initiated later in pregnancy

• Women’s message
  – Based on current data available DTG benefits- reduced side effects, improved efficacy and a high genetic barrier to resistance- outweigh its potential risks.
  – Blanket exclusions that deny women equitable access to this optimal HIV treatment are not warranted or justified.
Urgency to start ART

- **CD4 count <200 cells/µL**
  - Within 1 week if adherence counselling
- **PCP (PJP) and other OIs**
  - Within 2 weeks
- **Same day as diagnosis or receiving CD4 count.**
  - Pregnant or breast feeding women
  - HIV stage 4
  - Patient ready to start
  - Less LTFU

- **TB if CD4 count < 50 cells/µL**
  - Within 2 weeks
- **TB if CD4 count > 50 cells/µL**
  - Start 4-8 weeks
- **Cryptococcal meningitis**
  - Defer 4-6 weeks
- **TBM**
  - Defer 4-8 weeks
Failure of first line ART is common in patients dying from advanced HIV.

ART status

- ART naïve
- ART < 6 months
- ART > 6 months

ART > 6 months: median 3.6 years (IQR 1.7 – 6.7)
Conclusion

• Dolutegravir is the preferred anchor drug for 1st line ART
• CD4+ count no longer a gate keeper to ART
• IPT to all patients starting ART
• Accelerated ART initiation, including same day ART leads to improved outcomes
Questions?
ADVANCED TB
South Africa

AIDS-related deaths (all ages)

2018
- All ages estimate: 71,000
- Lower Estimate - Upper Estimate: 52,000 - 91,000

Source: UNAIDS Estimates 2019
South Africa

Co-management of TB and HIV treatment

Source: Global AIDS Monitoring 2018, WHO 2017 TB estimates
Time of death from hospital admission

- < 48 hours: 31%
- 1-2 weeks
- > 2 weeks
- 2-7 days

Inpatients die early: Early referral from clinics important. Rapid diagnosis and treatment at hospital level

David Maman, Rapport Hospitalisation CHK 2015/2017, Epicentre, 2017
% mortality by CD4 count

Slide Courtesy Dr Ian Proudfoot
**TB is the most common cause**

- Look for TB in all patients
- Start TB treatment rapidly
- Low threshold for empiric TB treatment

All patients with advanced HIV are strong TB suspects

All patients with TB have advanced HIV
TB remains a leading cause of hospitalization among PLHIV, particularly in Africa, South East Asia, and the Western Pacific regions, highlighting the important continuing contribution of TB as a major cause of serious HIV-associated morbidity.

**Explanation:**
- Late diagnosis of HIV
- Presentation with advanced immune deterioration
- Suboptimal adherence to ART & retention in care
Patient and provider delay in tuberculosis suspects from communities with a high HIV prevalence in South Africa: A cross-sectional study
Graeme Meintjes*1,2, Hennie Schoeman1, Chelsea Morroni3, Douglas Wilson1 and Gary Maartens4

Conclusion: Delay in TB diagnosis was more attributable to provider than patient delay, and provider delay was associated with increased mortality. Interventions to expedite TB diagnosis in primary care need to be developed and evaluated in this setting.
### Why cases are missed

<table>
<thead>
<tr>
<th>Why cases are missed</th>
<th>Underlying problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening may not be performed adequately</td>
<td>Care worker fatigue, variation in delivery,</td>
</tr>
<tr>
<td>Symptom screening may be performed but may miss cases</td>
<td>Symptom screen 84% sensitivity, 74% specificity, may be significantly lower in some settings</td>
</tr>
<tr>
<td>Appropriate diagnostic tests may not be requested after screening is performed</td>
<td>Application of subjective assessment of likelihood of disease by provider</td>
</tr>
<tr>
<td>Diagnostic tests used may miss cases – particularly extrapulmonary if using only pulmonary samples</td>
<td>Many sick people cannot produce sputum. Typical tests only applied to one sample type – sputum.</td>
</tr>
</tbody>
</table>
Neurological disease – ‘big 3’:  
• CNS TB  
• Cryptococcal meningitis  
• Toxoplasmosis

Other infections:  
• Bacterial meningitis  
• Other serious bacterial infections: community, nosocomial  
• Malaria  
• Parasite diarrhoeas

TB is the most common cause of mortality

Non-infectious causes:  
• Hypoglycaemia  
• Liver disease  
• Kidney disease  
• Electrolyte abnormalities  
• Drug side effects  
• Anaemia  
• Malnutrition

Kaposi’s sarcoma

Respiratory Disease – ‘big 3’:  
• Pneumocystis pneumonia  
• Pulmonary TB  
• Bacterial pneumonia

Underlying cause?

Slide courtesy Dr Ian Proudfoot
Diagnosis of TB

• **Clinical features**

• **Chest X-ray**

• Sputum smear for acid-fast bacilli (AFB)

• Sputum TB culture

• Sputum MTB/RIF Xpert

• Urine LAM (lipoarabinomannan)

• TB blood culture

• Tissue (culture / Xpert / AFB)

• *Urine Xpert*

  * Xpert test is not yet part of routine investigations, currently used in research in the public sector
1. Extrapulmonary TB more common
2. Chest X-Ray atypical (or normal)
3. More commonly smear negative
4. More rapid clinical deterioration

*All more so as CD4 declines

Sometimes need to make an empirical diagnosis of TB
Cavitatory disease seen in patients with CD4 > 200
Non-confluent opacification without cavitation in both lower zones

(CD4 = 57)
Large right mediastinal TB nodes  (CD4 = 16)
Common sites of extrapulmonary TB

- Lymphadenitis
- Abdominal
- Miliary / Disseminated
- Bone
- CNS
  - TBM
  - Tuberculomas
### Xpert MTB/RIF for EPTB

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sensitivity*</th>
<th>Specificity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node tissue or aspirate</td>
<td>85%</td>
<td>92%</td>
</tr>
<tr>
<td>CSF</td>
<td>55-80%</td>
<td>99%</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>17-44%</td>
<td>98%</td>
</tr>
<tr>
<td>Gastric aspirate</td>
<td>84%</td>
<td>98%</td>
</tr>
</tbody>
</table>

WHO: Inadequate data for other samples, therefore not included: ascites, pericardial fluid, urine, stool
*Compared to TB culture +/- composite reference standard
TB cervical lymphadenitis

Slide courtesy Prof G Meintjes
Tuberculomas
**Adult meningitis in a setting of high HIV and TB prevalence: findings from 4961 suspected cases**

Joseph N Jarvis¹,²,³,⁴*, Graeme Meintjes¹,⁴,⁵, Anthony Williams¹, Yolande Brown¹, Tom Crede¹, Thomas S Harrison³

*Jarvis et al. BMC Infectious Diseases 2010, 10:67*

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Neutrophils</th>
<th>Lymphocytes</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcal</td>
<td>16%</td>
<td>0 (0-3)</td>
<td>18 (3-73)</td>
<td>0.97 (0.5-1.7)</td>
</tr>
<tr>
<td>TBM</td>
<td>5%</td>
<td>4 (0-25)</td>
<td>60 (16-157)</td>
<td>2.09 (1.2-3.8)</td>
</tr>
<tr>
<td>Bacterial</td>
<td>4%</td>
<td>29 (5-420)</td>
<td>46 (14-106)</td>
<td>5.0 (2.7-5.0)</td>
</tr>
</tbody>
</table>
What to look for in the initial CSF results - in order of utility

- Gram stain- rarely +ve but when it is the diagnosis is confirmed
- CRAG- if +ve CM confirmed, unless previously treated
- VDRL- +ve result confirms neurosyphilis
- FTA-Abs- -ve result rules out neurosyphilis
- Glucose- if <2.5 increased likelihood of TBM or a bacterial cause but not definitive
- Protein- if around 1.5 suggests TBM, >5 suggests a bacterial meningitis but not definitive
- Cell counts- not very useful- normal results suggest ‘no meningitis’ but up to 5% of TB and bacterial meningitis cases may have normal findings.
- Very high polymorphs suggest bacterial or CMV

Slide courtesy Dr T Boyles
Association between tuberculosis dissemination and 12-week mortality
Drugs and Duration of Treatment

- Treatment of TB in PLHIV same as HIV-negative people
- DS-TB: 4 drug-susceptible regimen
  - INH, RIF, EMB, PZA for 2 months
  - INH & RIF for 4 months
- RAFA trial compared a higher dose of Rif (15 mg/kg) to (10mg/kg) in Rx HIV-associated TB
  - Found mortality benefit in patients with CD4+ <100 cells/mm³
- Guidelines have not yet recommended any changes
Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS

Figure 2. Cumulative Incidence of Paradoxical TB-Associated Immune Reconstitution Inflammatory Syndrome (IRIS).

A) Cumulative Incidence of TB-Associated IRIS at 12 Weeks

Relative risk, 0.70 (95% CI, 0.51–0.96)
P = 0.03 by chi-square test

39/120 (32.5%)
56/120 (46.7%)

B) Cumulative Incidence of TB-Associated IRIS over 84 Days

Hazard ratio, 0.61 (95% CI, 0.41–0.92)
P = 0.02

No. at Risk
Placebo 119 62 59 58 51
Prednisone 119 87 78 74 66

Prophylactic Prednisone

**Key Points:**
- Patients with a *microbiologically confirmed diagnosis of TB and improving on TB therapy with a CD4+ < 100*, on starting ART can be started on prednisone 40mg daily for 14 days followed by 20mg for 14 days.
- Prophylactic prednisone during the first 4 weeks after the initiation of ART in patients at high risk of TB-IRIS is associated with a 30% lower incidence of TB-IRIS.
- Prednisone use in this context is not associated with excess risk of severe infections, cancers, or adverse events.
- Prophylactic use of prednisone reduces severe TB-associated IRIS by 53%
47-year-old female with diagnosis of HIV CD4+ 84 on treatment for past 10 years FDC (Tenofovir/emtricitabine/efavirenz)
• Now diagnosed with PTB – started on treatment Rifafour (Rifampicin/Isoniazid/ethambutol/pyrazinamide)
• 1 weeks after starting TB treatment develops acute pancreatitis.
• TB therapy stopped
• Rechallenge back on Rifafour and does well.
• 12 days later has symptoms and lipase 297 U/L
• Recurrence of pancreatitis? which TB drug is the cause.
• Admitted to hospital and all TB meds stopped
• TB Drug rechallenge- Rifabutin/Isoniazid/ethambutol/pyrazinamide
A 34-year-old man with a CD4 count of 23 cells/mm$^3$ was diagnosed with tuberculosis (Xpert MTB/RIF). His tuberculosis symptoms had largely resolved by the time he started ART, 12 days after starting tuberculosis treatment. 3 days after starting ART, he developed anorexia, vomiting, nocturnal fevers, and worsening cough.

Lancet HIV 2019; 6:e463-74
• **TB is the most common cause of both admission and mortality**

  BUT......

  Usually there is more than one cause!!