Advanced HIV disease
Will it disappear with ART scale up?

DNDI meeting Cape Town
March 2018
IeDEA-COHERE: Results based on 951,855 adults from 55 countries after imputation of missing data

Does not include "re-starters" after interruption

In 2015 37% of people starting ART did so at CD4 cell count <200 cells/mm³
Temporal trends in the number of cases of laboratory-confirmed cryptococcosis and antiretroviral therapy coverage, Western Cape province, South Africa, 2007-2016

Adults, adolescents, children > 5 years
All children < 5 years considered advanced HIV disease
CD4 cell count < 200 cells/mm³ or WHO stage 3 or 4 event.
Includes both ART naïve individuals and those who interrupt treatment and return to care.
Advanced HIV will not disappear with ART scale up?
Evolution of CD4 < 100 cells/µL: national, KZN and WC

NHLS, South Africa
Adult total CD4 . DHIS data

TIER. Net data: MSF Eshowe KZN

CD4 count <100 by year
Western Cape Province

% of unique adults with CD4 < 50 by past history

Courtesy Meg Osler, Andrew Boulle, UCT/Cider. Submitted for publication
Defining patient groups

PLHIV < 200 CD4, stage III/IV

- Baseline CD4/staging
- Advanced disease screening package
- Accelerated ART initiation
- Prophylaxis package

- Baseline CD4/staging
- Advanced disease screening package/OIs management
- Referral as necessary
- Accelerated initiation
- Prophylaxis package

- IDEM + TRIGGERED CD4 + VL only if on cART

- TRIGGERED VL and CD4
  - VL > 1000 -> referral for extended OI screening/Management
  - Accelerated switch to 2nd line

Table 6.1. Dividing people living with HIV by clinical need for ART care

<table>
<thead>
<tr>
<th>People living with HIV</th>
<th>Care package elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>People presenting when well</td>
<td>Adherence and retention support</td>
</tr>
<tr>
<td>People with advanced disease</td>
<td>Clinical package to reduce mortality and morbidity</td>
</tr>
<tr>
<td>Stable individuals</td>
<td>Reduced frequency of clinic visits and community ART delivery models</td>
</tr>
<tr>
<td>Unstable individuals</td>
<td>Adherence support, viral load testing, switch to second- or third-line ART if indicated, monitoring for HIV drug resistance (HIV-DR)</td>
</tr>
</tbody>
</table>
Proposed actions to reduce Aids related mortality

Where: PHC level
What: management plan, up-referral criteria
When: Wk 2, mth 1, mthly for 6 mths
Who: Clinical office/ Nurses if ad-hoc training / expert client / hotline.
Welcome back clinics
Nsanje: 31/54 patients discharged with outcome at M2
- 5/54 admitted already (~10%)
For the 31 with an outcome
- 24 alive and waiting for next visit
- 5 died (~10%)
- 2 transferred out
Research gaps

- **Clinical strategy to further reduce mortality**
  - Switch to effective regimen -> DTG for 2\textsuperscript{nd} line
  - Improve systematic diseases diagnostic including new diagnostic tools (see TB)
  - Further develop human biomarkers to identify co-morbidities
  - Systematic pre-emptive treatment
  - Extended prophylaxis: TB, CM, PJP, sepsis
**LATTE-2 Study**

-RPV & CTG → Suppression maintenance in ARV-naive patients started on oral CTG+ABC/3TC x 20 wks

- THEN

1) Maintain Oral ARVs → 84% viral suppression
2) LA-CTG 400 mg plus LA-RPV 600 mg → 87%
   » 2 X 2 mL injections Q 4 weeks
3) LA-CTG 600 mg plus LA-RPV 900 mg → 94%
   - 2 X 3 mL injections Q 8 weeks
## Long-Acting Injs

### LATTE-2 Study – virological failure

<table>
<thead>
<tr>
<th>Arm</th>
<th>48 weeks</th>
<th>96 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (n=56)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Q4 week inj (n=115)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Q8 week inj (n=115)</td>
<td>8 (5 with VL btw 50 &amp; 200 ...which was not their def’n of VL failure)</td>
<td>4/5 of these «failures» were suppressed</td>
</tr>
</tbody>
</table>

Conclusion....further study needed and Q4 weeks went to Phase III

### What role for MSF?
PrEP: how to improve effectiveness?

New oral PrEP drugs and dosing strategies

Novel adherence strategies

van der Straten, et al., IAS 2017 #WEPEC0978.
HIV pipeline in clinical evaluation (viral suppression)

**Phase I**
- **Doravirine**
  - Oral nanoformulations
  - NNRTI
  - Merck

**Phase II**
- **ABX464**
  - Rev inhibitor
  - Abivax
- **GSK2838232**
  - Requires a booster
  - Maturation inhibitor
  - Viiv
- **Elsulfavirine (VM1500)**
  - NNRTI
  - Roche → Virol

**Phase III**
- **Albuviride**
  - (FB006M)
  - Entry inhibitor
  - Frontier Biotech
  - Filed with CFDA
- **Ibalizumab**
  - (TMB-355)
  - Entry inhibitor; mAb (not an ARV)
  - TaiMed Biologics, Theratechnologies
- **Bictegravir**
  - (GS-9883)
  - INI
  - Gilead, Filed with FDA

List not exhaustive. Shock-n-kill strategies, gene/cell therapies and non-oral immunotherapies are not included.

**Medicines Patent Pool.**
Last updated on: 5/30/2017

- **Fostemsavir**
- **Cabotegravir-LAI + Rilpivirine-LAI**
  - Maintenance strategy with oral induction
  - Viiv + Janssen
- **Cabotegravir-LAI**
  - (GSK-744; CAB)
  - INI
  - PrEP with oral induction
  - NIH; Viiv

- **Doravirine**
  - (MK-1439; DOR)
  - NNRTI
  - Merck

- **Second choice**
  - **MK-8591 (EFdA)**

**Clinical Trials**
- **HPTN 084**
  - CAB LA 600 mg
  - Phase 3 studies
  - 65 sites across 13 countries
  - Sponsored by NIH
  - Jointly funded by NIH, Bill & Melinda Gates Foundation, and Viiv

**Other**
- **Tobira**
- **CytoDyn**
- **TaiMed Biologics, Theratechnologies**
- **Theratechnologies**
- **Elsulfavirine (VM1500)**
  - NNRTI
  - Roche → Virol
- **Roche** → **Viriom**
- **PC-1005**
  - (MIV-150/zinc acetate)
  - NNRTI
  - Population Council
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- **PRO-140 (PA14)**
  - Not for X4-tropic HIV
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  - CytoDyn
- **Cenicriviroc**
  - (TBR-652; CVC)
  - Not for X4-tropic HIV
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  - Takeda → Tobira
- **VRC-01-LS**
  - bNAb
  - Rockefeller Univ.

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**Topical Microbicide**
- **Dapivirine**
  - (TMC120; DPV)
  - NNRTI
  - Janssen
- **MK-2048**
  - INI
  - NIH; Merck
- **PC-1005**
  - (MIV-150/zinc acetate)
  - NNRTI
  - Population Council
- **MK-8507**
  - Unknown MOA
  - Merck
- **Doravirine**
  - Oral nanoformulations
  - NNRTI
  - Merck
- **MK-8591 (EFdA)**
- **Rilpivirine-LAI**
  - (TMC278; RPV)
  - NNRTI
- **PrEP with oral induction**
  - NIH; ViiV

**Potential First-in-Class**
- **Cabotegravir-LAI + Rilpivirine-LAI**
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