Southern African HIV Clinicians Society
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13 - 16 April 2016
Sandton Convention Centre
Johannesburg

Our Issues, Our Drugs, Our Patients

www.sahivsoc.org
www.sahivsoc2016.co.za
Antiretroviral Therapy
Where we are and where we are going

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Professor Medicine
UNC Chapel Hill

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Disclosures

• Dr. Eron received research grants awarded to his institution from AbbVie, Janssen, and ViiV Healthcare, and has served as a consultant to AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare.
Goals of Antiretroviral Therapy

• Maintain or restore the health of people living with HIV-1 (PLWHIV) through suppression of HIV-1 replication

• Minimize or eliminate short and long-term adverse effects of the therapy

• Have therapies that are accessible to all PLWHIV

• Prevent transmission of HIV-1 to others via any route of exposure
We have big goals!

90% diagnosed
90% on treatment
90% virally suppressed

15.8 million PLWHIV on ART in 2015

90-90-90 An ambitious treatment target to help end the AIDS epidemic

Impact of the 90-90-90 target on HIV infections and AIDS-related deaths, 2016-2030

CAN ANTIRETROVIRAL THERAPY HOLD UP ITS END OF THE BARGAIN – 90% SUPPRESSED?
Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

Published July 20, 2015 at NEJM.org
HPTN 052: Reduced Risk of Partner Infection

• ART offered to all index pts in delayed ART arm from May 2011 after interim results
  – 84% of pts in delayed ART arm had initiated ART at Yr 1 and 98% prior to study closure
• 8 linked HIV infections diagnosed after seropositive patient started ART
  – All occurred before or soon after initiation or after virologic failure
• No linked HIV transmissions observed when index participant stably suppressed on ART

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<th>Partner Infections, n (rate/100 PY)</th>
<th>Overall (April 2005 - May 2015)</th>
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<td>Early (4314 PY F/U)</td>
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<th>Risk Reduction With Early ART, %</th>
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<tr>
<td>All infections</td>
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<td>Linked infections</td>
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Cohen MS, et al. IAS 2015. Abstract MOAC0101LB.
WHY IS ART SO SUCCESSFUL IN PATIENTS WHO HAVE ACCESS

Potent, Relatively simple (multiple single tablets regimens)
Favorable PK
Well tolerated
Shift To Integrase Inhibitor-based Therapy

Initial Antiretroviral Therapy

1,773 patients initiating ART between 1996 and 2014 in the UCHCC, follow-up through 2015

bPI = LPV/r, DRV/r or ATV/r therapy
Other = includes unboosted PI and other bPI combinations

Courtesy of Thibaut Davy and Sonia Napravnik
In CNICS cohort integrase inhibitor use was strongly associated with HIV RNA suppression in multivariate analysis see poster 1034 Simoni et al.
Continued Improvement in Currently Available ART Classes

• Dolutegravir
  – Once daily, unboosted,
  – Limited drug interactions, high barrier to resistance

• Tenofovir alafenamide fumarate
  – Equal efficacy with TDF containing therapies, less bone toxicity and renal tubular effects
  – Smaller mg dosing (25 mg)
  – Use in renal dysfunction (CrCl down to 30 cc/min)
  – Activity against NRTI-resistant variants (?)

• Two drug therapy
  – Less expensive, fewer toxicities?
Elvitegravir/cobi/TAF/FTC vs. Elvitegravir/cobi/TDF/FTC
Phase III treatment naïve study: 48 week results

- E/C/F/TAF was non-inferior to E/C/F/TDF at Week 48 in each study
  - 93% E/C/F/TAF vs 92% E/C/F/TDF (Study 104)
  - 92% E/C/F/TAF vs 89% E/C/F/TDF (Study 111)

ART to Decrease Long-term Toxicity

Switch from Tenofovir DF to Tenofovir alafenamide–containing therapy in patients with suppressed plasma HIV RNA levels.

Improvements in proximal renal tubular function

Study 112: Week 96 Changes After Switch to E/C/F/TAF in Patients With Renal Impairment

- Median eGFR change after E/C/F/TAF switch
  - CDK-EPI Cr: 1.0 mL/min (n=158)
  - CDK-EPI CysC: 3.9 mL/min (n=157)
- Significant improvements after E/C/F/TAF switch ($P<0.05$)
  - Proteinuria
  - Renal tubular function
  - Spine and hip bone mineral density
- Maintained HIV RNA <50 copies/mL: 88%
  - Virologic failure: 2% (5/242)
  - No virologic data: 10% (23/242)
- These 96-week data support the renal and bone safety of E/C/F/TAF in HIV patients with renal impairment (eGFR 30-69 mL/min)

GARDEL: Dual ART Noninferior to Triple ART in Tx-Naive Pts at Wks 48 and 96

- Phase III, international, open-label, randomized study

- Safety and tolerability also similar between treatment arms

Two drug ART to Achieve and Maintain Suppression
Dolutegravir plus 3TC 24 week data
PADDLE Study

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From week 8 onwards all patients had pVL < 50 copies/mL

Figueroa et al (Pedro Cahn) 15th European AIDS Conference 2015
RESISTANT HIV-1 WILL ALWAYS BE WITH US

Four to eight decades of therapy!
Previous exposure to suboptimal treatment developed world-wide
Limited monitoring of virologic response world-wide
Transmitted drug resistance
Resistance in Developing World

- Second-line study: NNRTI/NRTI first line virologic failure – 15 countries – majority of participants from Africa or Asia
  - Baseline resistance - 492 participant samples


Published Online January 28, 2015 – Abstract 503
New Agents for Resistant HIV-1

- Integrase Inhibitors
  - Dolutegravir (approved)
  - GS-9883 (Phase III)

- N(t)RTI
  - TAF (approved)
  - EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine)(Phase I-II)

- NNRTI
  - Doravirine (Phase III)

- Maturation Inhibitors
  - BMS 955176 (Phase II)

- Attachment inhibitors
  - BMS 663068 -> 626529 (Phase III)

- Broadly neutralizing monoclonal antibodies

New Targets: e.g. LEDGF, combination entry, additional maturation sites, HIV-1 RNA processing
Maturation Inhibitors (MIs): BMS-955176 Mode of Action

Lataillade et al. CROI 2015, Abstract 114LB
Maturation Inhibitors (MIs): BMS-955176 Mode of Action

Lataillade et al. CROI 2015, Abstract 114LB
Maturation Inhibitors (MIs): BMS-955176 Mode of Action

- BMS-955176 inhibits the last protease cleavage event between capsid (CA) protein p24 and spacer peptide 1 (SP1) in Gag, resulting in the release of immature, non-infectious virions.


Lataillade et al. CROI 2015, Abstract 114LB
**BMS-955176: Median Change in HIV-1 RNA over Time**

- Median change in HIV-1 RNA from baseline to Day 11 reached $\sim 1.4 \log_{10} \text{c/mL}$

See Abstract 425, 464
BMS-626529 Attachment Inhibitor: Proposed Mechanism of Action

1. Langley DL et al. Manuscript in development.
AI438011: BMS-663068 Monotherapy Substudy: Mean Change in HIV-1 RNA from Baseline*

*Error bars represent standard error of the mean.

Lalezari et al CROI 2014 abstract 86
Maintaining therapy for Life in all PLWHIV

• Adherence
  – Hard to reach populations, substance use, depression, children, adolescents ........

• Life Chaos
  – Travel, dislocation for work or safety, surgery, drug interactions, pill fatigue, patient preference ......

Long acting antiretroviral Therapy!
Cabotegravir LA and Rilpivirine LA Nanosuspensions

- Drug nanocrystal suspended in liquid = nanosuspension
- Nanomilled to increase surface area and drug dissolution rate
- Allows ~100% drug loading vs. matrix approaches for lower inj. volumes

**GSK744 200mg/mL**

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**TMC278 300mg/mL**

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Mean Plasma cabotegravir Concentration-Time Profiles Following Single 100-800 mg LAP Doses (200mg/mL nanosuspension)

Differences observed between split and unsplit dosing

LATTE-2: Cabotegravir IM + Rilpivirine IM for Long-Acting Maintenance ART

- Multicenter, open-label phase IIb study
  - Primary endpoints: HIV-1 RNA < 50 c/mL by FDA snapshot, PDVF, and safety at maintenance Wk 32

**Induction Phase***

| ART-naive HIV-infected pts with CD4+ cell count > 200 cells/mm³ (N = 309) |
| C 30 mg PO QD + ABC/3TC |
| Wk 16: RPV PO Added |
| Wk 20 |

**Maintenance Phase**

| Wk 1 |
| Wk 32 primary analysis; dose selection |
| Wk 96 |

| CAB 400 mg IM + RPV 600 mg IM Q4W (n = 115) |
| CAB 600 mg IM + RPV 900 mg IM Q8W (n = 115) |
| CAB 30 mg PO + ABC/3TC PO QD (n = 56) |

*Pts with HIV-1 RNA < 50 c/mL from Wk 16 to Wk 20 continued to maintenance phase. In snapshot induction analysis, 14 pts had virologic nonresponse and 13 pts had no virologic data in window, including 6 pts who discontinued for AEs or death and 7 pts who discontinued for other reasons.


Slide credit: clinicaloptions.com
Two Drug ART Maintains Suppression
Latte: Cabotegravir (InSTI) + rilpivirine maintenance vs. EFV-based therapy

Figure 2: Proportion of patients with HIV-1 RNA concentration of less than 50 copies per mL by visit in the intention-to-treat exposed population. Error bars indicate 95% CI.
LATTE-2 Week 32 Primary Endpoint: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

*Met pre-specified threshold for concluding IM regimen is comparable to oral regimen (Bayesian posterior probability >90% that true IM response rate is no worse than -10% compared with the oral regimen).

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.
4′-ethynyl-2-fluoro-2′-deoxyadenosine (EFdA) MK8591

- EFdA (MK-8591) is a nucleoside reverse transcriptase translocation inhibitor (NRTTI)

- Sub-nanomolar potency in vitro\(^1\) and prolonged suppression of SIV in macaque model\(^2\)

- Prolonged persistence of triphosphate form in PBMC and macrophage

- Potential for once weekly dosing (Friedman et al Abstract 437LB)

- Long-acting formulations under development (Grobler et al Abstract 98)

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\(^1\)Michailidis et al J Biol Chem 284: 35681-91; 2009  \(^2\)Murphey-Corb et al AAC 56:4707-12; 2012
MK-8591: Reduction in HIV RNA for at Least 10 Days After Single Oral Dose

- Open-label study (n=6)
  - Treatment-naïve males
  - CD4 >500 cells/mm³
- MK-8591 (NRTI)
  - Single, 10-mg oral dose
- Intracellular MK-8591-TP in PBMC
  - T1/2 (geometric mean): 103 hours
- No evidence of resistance out to day 10
- HIV RNA reduction (log_{10} copies/mL)
  - Day 7: 1.67
  - Day 10: 1.78
- Generally well tolerated

TP: triphosphate.

Friedman E, et al. 23rd CROI. Boston, 2016. Abstract 437LB.
BROADLY NEUTRALIZING ANTIBODIES

Can they be harnessed as therapy?
Broadly Neutralizing Antibodies as Therapy

• Can they be used successfully as therapy?
  – Single antibodies lack needed breadth\textsuperscript{refs}
  – Combinations of antibodies with differing targets
    • Anti-CD4 binding plus anti-V3 or V2 plus others?
  – Modifiable to increase half-life
  – Bispecific antibodies
  – Antibody-like inhibitors (e.g. eCD4-Ig)
  – In combination with long-acting antiretrovirals?

• But...
  – Cumbersome delivery, increasing potency = decreasing dose
  – Virus escape – frequency of monitoring
  – Anti-idiotype or other inhibitory antibodies
  – Advantages over antiretrovirals – other than being sexy?

Antiretroviral Therapy: The Next Generation?

• Implantable (and removable) combination antiretrovirals

• Vectored delivery of combinations of antibody-based therapy or protein based therapy

Recombinant AAV (rAAV) features:
- Transfects both dividing & non-dividing cells
- No host-genome integration & Stable Expression
- Ease to produce at high viral titer (Helper Free)
- Do not elicit significant immune response in vivo
- Can be used for in vivo gene deliveries
Antiretroviral Therapy: The Future

- HIV-1 discovered
- ZDV monotherapy
- ZDV/3TC
- Triple Drug Therapy
- Single Tablet Regimens
- The Integrase Era
- Long Acting Injectable?

Timeline:
- 1983
- 1987
- 1995
- 1996
- 2006
- 2012-13
- 2017
- 2020
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