CROI Conference Review: 30 years of HIV

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Objectives

- Discuss advances on HIV prevention strategies
- Appraise novel therapies for the treatment of HIV and HCV infections
- Integrate screening and treatment of common co-morbidities and HIV complications
National HIV/AIDS Strategy
Goals associated with Targets by 2015

- HIV incidence reduction
  - Lower annual number of new infections by 25%
  - Lower annual transmission rate by 30%

- Increase access to and quality of care
  - Increase to 85% proportion if patients linked to care within 3 months of diagnosis

- Reduce HIV related disparities
  - Increase by 20% proportion of PLWHA with undetectable VL among AA, Latinos and MSM

Mermin, Oral Session 5; 18th CROI 2011; Boston, MA
AIDSpolicy@who.eop.gov
Prevention Science in the US

- ≥ 1.1 million people living with HIV
  56,000 new infections – 16,000 deaths = 40,000 net increase in PLWHA
    - 54% live in 5 states
    - 90% in 23 states
    - 53% in MSM, 12% IDU, 31% Heterosexual contact
    - 45% in AA, 35% Whites, 17% Hispanics/Latinos

- MSM are 40X more likely to be infected
- AA 8X, Latinos 3X
- Estimated life expectancy on ART=35 years
- Since the beginning of the epidemic over 350,000 cases of HIV averted

Mermin, Oral Session 5; 18th CROI 2011; Boston, MA
Community Viral Load (cVL) may have an impact on transmission.

- Since 1996, HIV incidence declined by 68% per each log decline in cVL.
- HIV incidence declined by 5% for each 1% increase in proportion of those taking ART.

**cVL Definition:** Aggregate biological measure of Viral Load for a particular geographic location and for a particular group for people who share socio-demographic characteristics.

Mermin, Oral Session 5; 18th CROI 2011; Boston, MA
Combination Prevention

Biomedical Interventions
- PEP
- PrEP
- Microbicides
- Vaccines

Community Interventions
- Change in attitudes, norms and values of entire community/target population
- Change in Social and Environmental context
- Empowerment

Testing and Linkage to Care
- VCT Centers
- HPTN TLC-Plus
- PMTCT Centers

Individual and Small Group Interventions
- Diffusion of Evidence Based Interventions Project
- Healthy Relationships
- SISTA
- Willow
- Voices/Voces
- Personalized Cognitive Counseling
- PWP
- Others

Structural Interventions
- Comprehensive sex education and Access to Male and Female Condoms
- Syringe Exchange Programs
- Health Care Access
- Stable Housing

Mermin, Oral Session 5; 18th CROI 2011; Boston, MA
High Impact Prevention

Effectiveness and Cost:
- Efficacy (RCT) vs.
- Effectiveness (Real world)
- Intervention Uptake
- Access to target Population
- Cost-Effectiveness

Feasibility of Full Scale Implementation

Interaction and Targeting

Coverage of Target Population

Science of Implementation
- Choosing
- Mixing
- Maximizing Impact

Prioritizing

Mathematical Models  Research  Programs

Mermin, Oral Session 5; 18th CROI 2011; Boston, MA
Pre-Exposure Prophylaxis

iPREX Follow up

- No ↓ in condom use
- No major side effects
- No bone abnormalities
- Effectiveness related to adherence
- More cost-effective than early initiation of ART in infected partner in sero-discordant couples
- Effective even in resistant variants

Microbicicides

- Raltegravir Gel
  - Stable,
  - 100% protection in macaques
  - Combination with other products?
- TDF Rectal Gel
  - Safe, tolerable
  - Likely to be acceptable

Dobard, Anton, Garcia-Lerma, Park Oral Session 8; 18th CROI 2011; Boston, MA
Linkage to care

• HIV care and treatment programs should aim to achieve:
  • Early diagnosis of HIV infection
  • Prompt enrolment in Pre-ART care
  • Appropriate monitoring and care prior to ART eligibility
  • Timely initiation of ART
  • Survival through early years on ART
  • Lifelong retention in treatment program

Rosen; 18th CROI 2011; Boston, MA
Linkage to care

- Paucity of data but published evidence shows:
  - 55% of HIV positive are staged &/or enrolled in pre-ART care
  - About ½ of those enrolled in pre-ART care are retained until ART initiation or other endpoint
  - About ⅔ of those who are in care at ART eligibility initiate treatment
  - *Only ⅓ of those who test HIV positive are retained in care continuously*

- Mortality of 22.5% at 1 yr among ART eligible patients lost to follow up in Uganda

- Possible interventions include:
  - Reducing patient costs
  - Increasing patients benefits
  - Point of care CD4 counts

Rosen; 18th CROI 2011; Boston, MA
Risk to be Lost to Follow-up

- Telephone only or no dedicated staff for out-reach
  RR = 3.36 (1.72, 6.57),

- Public means/ bicycle or foot for outreach
  RR = 3.12 (1.41, 6.88)

- Imitating LTFU search 30 days after missed visit vs. less than 30 days: 2.32 (1.26, 4.24)

- Initiating ART or TMP/SMZ, regardless of CD4: 84% retained vs. 63%, p <0.001, adjusted HR 2.64 (1.95, 3.57)

Ahonkai, Braitstein, Kohler, Achieng; Session 16, Themed Discussion; 18th CROI 2011; Boston, MA
Adherence and Retention in Care

Sub-Saharan Africa

- 40% attrition in Sub-Saharan Africa
  - 11% have interrupted care but remain in treatment
  - Incidence of Lost to FU = 16.5 (16.2-16.9)
- Adherence Interventions
  - Telephone messages
  - Support groups
  - Provider pill counts in front of the patient

Pill Counts by Clinicians Improve Time to Failure

Ahonkai, Braitstein, Kohler, Achieng; Session 16, Themed Discussion; 18th CROI 2011; Boston, MA
ARV Strategies
Long term Efficacy of DRV/r Monotherapy in Patients with HIV-1 Viral Suppression in the MONOI-ANRS 136 Study: Results at 96 Weeks

Darunavir/r (DVR/r) monotherapy vs. Standard Triple-drug approach with success rate over 90% at 48 weeks. At week 48 patients were allowed to switch to DRV/r 800/100 mg once daily and were then followed until week 96

Failures:
Overall 9 Virologic Failures between weeks 48-96
• 2/5 in mono therapy arm
• 4/4 in Triple arm between week 48-96)
No emergence of DRV resistance mutations

Conclusions: At week 96, the rate of Virologic suppression did not differ between the 2 strategies

Valantin, Poster 534; 18th CROI 2011; Boston, MA
Results from a Single Arm Study of DRV/r + RAL in Treatment-naïve HIV-1-infected Patients (ACTG A5262)

**Multicenter, single arm, open label, 52 wks pilot study**
HIV-1 Infected 18 years or older
ARV Naïve, VL >5,000 copies
No more than one DRV resistance-associated mutations

**Primary Objective:**
To estimate the cumulative proportion of subjects experiencing Virologic Failure (Week 24)

**Results:**
No DRV resistance mutations
IN resistance 4/23 genotyping samples: N155H (1), N155HN (2), Q148QR and N155HN (1)
No unexpected toxicities occurred

<table>
<thead>
<tr>
<th>Virologic Failure (VF)</th>
<th>N=112</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Period</strong></td>
<td><strong>VF</strong></td>
</tr>
<tr>
<td>Week 24</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>16%</td>
</tr>
<tr>
<td>Week 48</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>26%</td>
</tr>
</tbody>
</table>

**Conclusions:** DRV/r + RAL was effective and well tolerated, but those with BL VL >100,000 copies/ml had more VF and Integrase resistance

Taiwo, Poster 551; 18th CROI 2011; Boston, MA
Long Term Follow Up of Patients Receiving RAL, ETV, and DRV/r in the ANRS 139 TRIO Trial

Phase II Non-Comparative Multi Center Trial
Follow up of virologic suppression
ARV experienced(*), but naïve to study drugs

Endpoint: % of patients with HIV-1 RNA <50 at weeks 24, 48 and 96

Results: 5% VF after week 48, all VF had <400 copies; 4/5 <50 copies thereafter.
HIV-1 RNA was <50 copies/ml in 88% of patients at week 96
No significant AE

Conclusion:
RAL +ETV + DRV/r + OBT regimen is highly efficacious and safe at 2 years of continuous treatment.
VF was rare and occurred at low level viremia

Characteristics N=100

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=100</th>
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<tbody>
<tr>
<td>Male</td>
<td>89</td>
</tr>
<tr>
<td>Age</td>
<td>45</td>
</tr>
<tr>
<td>H/O ARV, (ys)</td>
<td>13</td>
</tr>
<tr>
<td>CD4+ Nadir</td>
<td>80</td>
</tr>
<tr>
<td>CD4+ Wk-0</td>
<td>258</td>
</tr>
<tr>
<td>HIV-1 RNA</td>
<td>4.2</td>
</tr>
<tr>
<td>Clinical Stage C</td>
<td>41</td>
</tr>
</tbody>
</table>

Fagard, Poster 549; 18th CROI 2011; Boston, MA
HAART at 15
What Does the future Hold?

Patrick Yeni, MD
Hospital Bichat Claude Bernard
University Paris
France
Better tolerated than in 1996, but associated with significant toxicity.

Recommended early in the course of HIV infection, but does not reach a majority of patient in need.

Is Highly effective, but in patients with plasma HIV RNA <50 c/ml:

- HIV infection is not cured.
- Interruptions are followed by rebound viremia
- Low level viremia persist in 80% of patients.
- Chronic T cell activation and inflammation persist.
The Future of HIV Therapy: When will research translate into clinical practice?

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SHORT-TERM</strong></td>
<td>New ARV drugs from existing classes</td>
</tr>
<tr>
<td></td>
<td>New co-formulation</td>
</tr>
<tr>
<td></td>
<td>Alternative strategies for ARV therapy</td>
</tr>
<tr>
<td><strong>MID-TERM</strong></td>
<td>New ARV drugs from new classes</td>
</tr>
<tr>
<td></td>
<td>Complementary, non ARV-containing therapy</td>
</tr>
<tr>
<td><strong>LONG-TERM</strong></td>
<td>Active and safe drugs to target latent latently infected resting memory CD4 T cells (anti-latency approach)</td>
</tr>
<tr>
<td></td>
<td>Active and safe therapy, derived or not from gene therapy to prevent or silence HIV infection of T cells</td>
</tr>
</tbody>
</table>

Yenni; Session 20; Symposium; 18th CROI 2011; Boston, MA
15 Years of HAART
The tracks to the future

New ARV and co-formulations
- **Rilpivirine** (NNRTI), co-formulated with TDF/FTC
- **Elvitegravir**: Once/day Integrase Inhibitor
- **Cobicistat**: New pharmacologic enhancer (booster) CYP3A Inh
- **Dolutegravir**: Integrase Inhibitor

New Strategies for ARV Therapy
- Identify different class for 3rd drug (i.e. 2NRTI + CCR5 Inhibitor)
- Replace the 2NRTI backbone (i.e. PI/r + NNRTI or PI + II)
- Elaborate a fully alternative regimen (NNRTI + PI + II)

Complementary, Non-ARV containing Therapy
- Strategies to minimize immune dysfunction and/or chronic inflammation: R-hIL-7, Maraviroc, Rifaximin
- Drugs with anti-inflammatory activity: ASA, HMG-CoA Inhibitors (statins)
- Inhibition of the Tox Pathway
- Others: Telomerase-based, anti-fibrosis

Yenni; Session 20; Symposium; 18th CROI 2011; Boston, MA
Some ARV agents in active phase I/II development

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Agent</th>
<th>Drug Company</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Festinavir (E-d4T, formerly OBP-601)</td>
<td>BMS</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>CMX-157 (a lipid conjugate of TDF)</td>
<td>Chimerix</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>GS-7340 (a prodrug of TFV)</td>
<td>Gilead</td>
<td>I</td>
</tr>
<tr>
<td>NNRTI</td>
<td>GSK-2248761</td>
<td>ViiV (GSK)</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Lersivirine (UK-453061)</td>
<td>ViiV (Pfizer)</td>
<td>II</td>
</tr>
<tr>
<td>PIs</td>
<td>CTP-518 (a deuterium-modified ATV)</td>
<td>Concert Pharma</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>TMC-310911</td>
<td>Tibotec</td>
<td>II</td>
</tr>
<tr>
<td>CCR5 Inhibitor</td>
<td>TBR-652 (also CCR2 inhibitor)</td>
<td>Tobira Therapeutics</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>PRO 140 (a CCR5 mab)</td>
<td>Progenics Pharma</td>
<td>II</td>
</tr>
<tr>
<td>Other Targets</td>
<td>BMS-663068 (Attachment Inhibitor)</td>
<td>BMS</td>
<td>II</td>
</tr>
<tr>
<td></td>
<td>Ibalizumab (a CD4 monoclonal Antibody)</td>
<td>TaiMed Biologics</td>
<td>II</td>
</tr>
</tbody>
</table>

Yenni; Session 20; Symposium; 18th CROI 2011; Boston, MA
Sources of Infection for Persons with Hepatitis C

- Injecting Drug Use 60%
- Transfusion 10% (before screening)
- Unknown 10%
- *Nosocomial
- Health-care worker
- Perinatal

Prevalence of HCV/HIV Co-Infection in US

- HCV - 4 million
- HIV - 1 million
- HIV/HCV co-infection - 400,000
- HCV related mortality - 10,000/yr

Source: Centers for Disease Control and Prevention

Waldrep et al. Pharmacotherapy 2000
Staples et al. CID, 1999
Chamot et al. AIDS, 1990
HCV/HIV Treatment:
Who should be considered for treatment?

- **CD4>500**: treat
  - goal: SVR

- **CD4 200-500**: consider
  - goal: SVR or to:
    - reduce risk of HAART related hepatotoxicity
    - reduce risk of progression to ESLD
  - may benefit from therapy if plasma HIV RNA <5000 copies/ml

- **CD4<100**: do not treat
  - therapy should not be initiated in any person with an active opportunistic infection

Boceprivir (BOC) + P/R for Treatment-naïve HIV/HCV Coinfected Patients with HCV Genotype-1: SPRINT-2

- **Boceprivir (BOC)** is an HCV HNS3 Protease Inhibitor
- Phase 3, Double Blind RCT
- 4 week Lead-in (LI) with Peg-IF/RBV (P/R) followed by:
  - Arms 1: 44 weeks P/R
  - Arm 2: Response Guided Therapy (RGT), if viremia in weeks 8-24, continue 20 weeks with P/R
  - Arm 3: 44 weeks BOC + P/R
- Non-blacks and blacks enrolled separately

**Conclusions:** BOC/P/R significantly increased Sustained Virologic response (SVR) in both the RGT and the 48-week treatment arms over standard of care by ~70%. BOC was well tolerated. No racial differences identified

*Sulkowski, poster#115, 18th CROI 2011*
HCV RESPOND-2 Final Results: High Sustained Virologic Response among Genotype-1 Previous Non-responders and Relapsers to pegIFN/RBV when Retreated with BOC + PEGINTRON/RBV

<table>
<thead>
<tr>
<th>NAME</th>
<th>CLASS</th>
<th>RESPONSE RATE</th>
<th>RECOMMENDED REGIMEN</th>
<th>LENGTH OF TREATMENT</th>
<th>SPECIAL CONSIDERATIONS</th>
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<tbody>
<tr>
<td>Boceprevir</td>
<td>HCV Protease Inhibitor</td>
<td>67% SVR Arm 3</td>
<td>BOC/P/R Arm 3</td>
<td>48 week</td>
<td>Genotype 1 P/R treatment failure patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>59% SVR Arm 2</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>21% SVR Arm 1</td>
<td></td>
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</tr>
<tr>
<td><strong>Arm 1</strong></td>
<td>(control) P 1.5microg/kg +R 600 to 1400 mg/day x48 week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arm 2</strong></td>
<td>P/R 4 Week then P/R+800mg BOC 3X/day for 32Week+/‐ P/R 12 Week</td>
<td></td>
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</tr>
<tr>
<td><strong>Arm 3</strong></td>
<td>P/R 4 Week then P/R+800 BOC 3 X/DAY for 44 week</td>
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</tbody>
</table>

P=Pegylated Interferon Alpha-2
R=Ribavirin
BOC=Boceprevir
SVR=Sustained virological response

Gordon; Poster#116, 18th CROI 2011
## Novel HCV Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Drug-drug Interactions</th>
<th>Metabolism and Clearance</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir</td>
<td>HCV Protease Inhibitor</td>
<td>EFV ↓ level</td>
<td>Hepatic mediated Reversible CYP3A4 inhibitor</td>
<td>Boceprevir+ Pegylated Interferon Alpha+ Ribavirin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ketoconazole ↑ exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telaprevir</td>
<td>HCV Protease inhibitor</td>
<td>EFV ↓ level by 47%</td>
<td>Substrate and inhibitor of CYP3A</td>
<td>In combination with Pegylatedi Interferon and Ribavirin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RTV -boosted PI s ↑ exposure</td>
<td></td>
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Kassera.C et al, poster# 118, 18th CROI 2011
Heeswijk.RV, et al, poster #119, 18th CROI 2011
HCV Summary

- 1/3 of patients with HIV have HCV
- HCV progression may be faster in HIV-infected patients
- HCV diagnosis requires HCV RNA because HCV Ab may not be reliable
- HCV Management
  - HCV genotype (2,3 more favorable than 1,4)
  - Ultrasound
  - Evaluate for cirrhosis
- Standard of care has been Pegylated Interferon and Ribavirin in appropriate pts
- Boceprevir/ Pegylated Interferon 2-alpha/Ribavirin (BOC/P/R) increased SVR significantly compared with standard of care P/R therapy and also was effective in non-responders and after relapse in patients with Genotype 1.
Opportunistic Infections

Cryptococcal Meningitis & Tuberculosis
Cryptococcus meningitis

- Amp B and 5-Flucytosine remain standard of care
- Amp B (5 days) with high dose fluconazole (1200mg), associated with outcomes similar to 2 week Amp B with less toxicity
- Amp B (.7 mg/kg) plus either fluconazole (800 mg) or voriconazole (300 mg) similar survival and crypto clearance as Amp B flucytosine
- INF-gamma is associated with more rapid CSF clearance
- Survival not associated with time to ART initiation
Cryptococcus meningitis

- IRIS associated with 2 week fungal burden (log CFU/ml CSF) but not time to ART

- Baseline fungal burden, weight and abnormal mental status predict 10-week mortality

- Unanswered questions:
  - Optimal time to ART initiation
  - IRIS – early detection and treatment
  - Serum CRAG screening in patients with CD4 <100 - what is the optimal therapy for asymptomatic disease and what would be the public health implications

Bicani ; Loyse; Jarvis; Muzoora; 18th CROI 2011; Boston, MA
TB Treatment

- **STRIDE STUDY**
  - 806 subjects with proven or presumptive TB randomized to either
    - Early ART (2 weeks after TB diagnosis)
    - Late ART (4-8 weeks after TB diagnosis)
  - Lower rates of AIDS events, IRIS and death in subset with CD4 count < 50 cells/mm in the early treatment arm

- **SAPiT STUDY**
  - 251 subject with smear positive TB and CD4 count < 500 cells/mm3 were randomized to either
    - Early Art (within 4 weeks of initiation of TB therapy)
    - Late ART (4-8 weeks after initiation of TB therapy)
  - Subjects with CD4 < 50 had longer AIDS free survival but increased rates of IRIS with early ART
  - Subjects with CD4 count > 50 had no differences in survival but less toxicities with and fewer drug switched with late ART

Havlir; Karim; Session 9; Symposium; 18th CROI 2011; Boston, MA
TB Treatment

- Recommended dose of Rifabutin with protease inhibitors is 150 mg three times per week
- 16 patients on TB therapy including rifabutin before and after the introduction of LPR/r were randomized to receive either standard (rifabutin 150/3 times/week) or daily dosages of rifabutin
- Rifabutin levels in the three times weekly arm were sub-therapeutic while levels in the daily arm were in the therapeutic range
- Both dosages were well tolerated
TB Diagnosis: Gene Xpert MTB/RIF

- Xpert MTB/RIF
  - Real time PCR of MTB rpoB gene region
  - Detect MTB and common RIF resistant mutations
  - Does not detect resistance to other drugs
  - Fully automated, only 2 manual steps
  - Available only for sputum samples
  - Expensive for resource limited settings

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 sputum</td>
<td>92.2 %</td>
<td>99.2%</td>
</tr>
<tr>
<td>3 sputa</td>
<td>97.6%</td>
<td>98.1%</td>
</tr>
</tbody>
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Dorman; Session 48; Symposium; 18th CROI 2011; Boston, MA
Urine Assay for Mycobacterial Lipoarabinomannan (LAM)

- **LAM (lipoarabinomannan)**
  - Component of MTB cell wall lipopolysaccharide
    - Released from metabolically active or degraded MTB and excreted into the urine
    - Can be measured by an ELISA assay
    - Previously demonstrated to have the best utility in HIV patients with CD4 cells < 200

- **Clinical Studies: Screening for TB at ambulatory site**
  - 443 patients attending HIV clinic were screen for TB, 30 were found to be smear positive
  - Best results were in patients with CD4 < 50 (PPV= 90%, NPV = 55%)
  - Conclusion: not suitable for mass screening but may be useful in patients with very low CD4 cells

Dorman; Gounder; Session 48; Symposium; 18th CROI 2011; Boston, MA