



Texas/Oklahoma
AIDS Education & Training Center

CROI Conference Review: 30 years of HIV



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and Training Center Faculty



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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 of 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
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Prevention Science in the US

- \geq 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



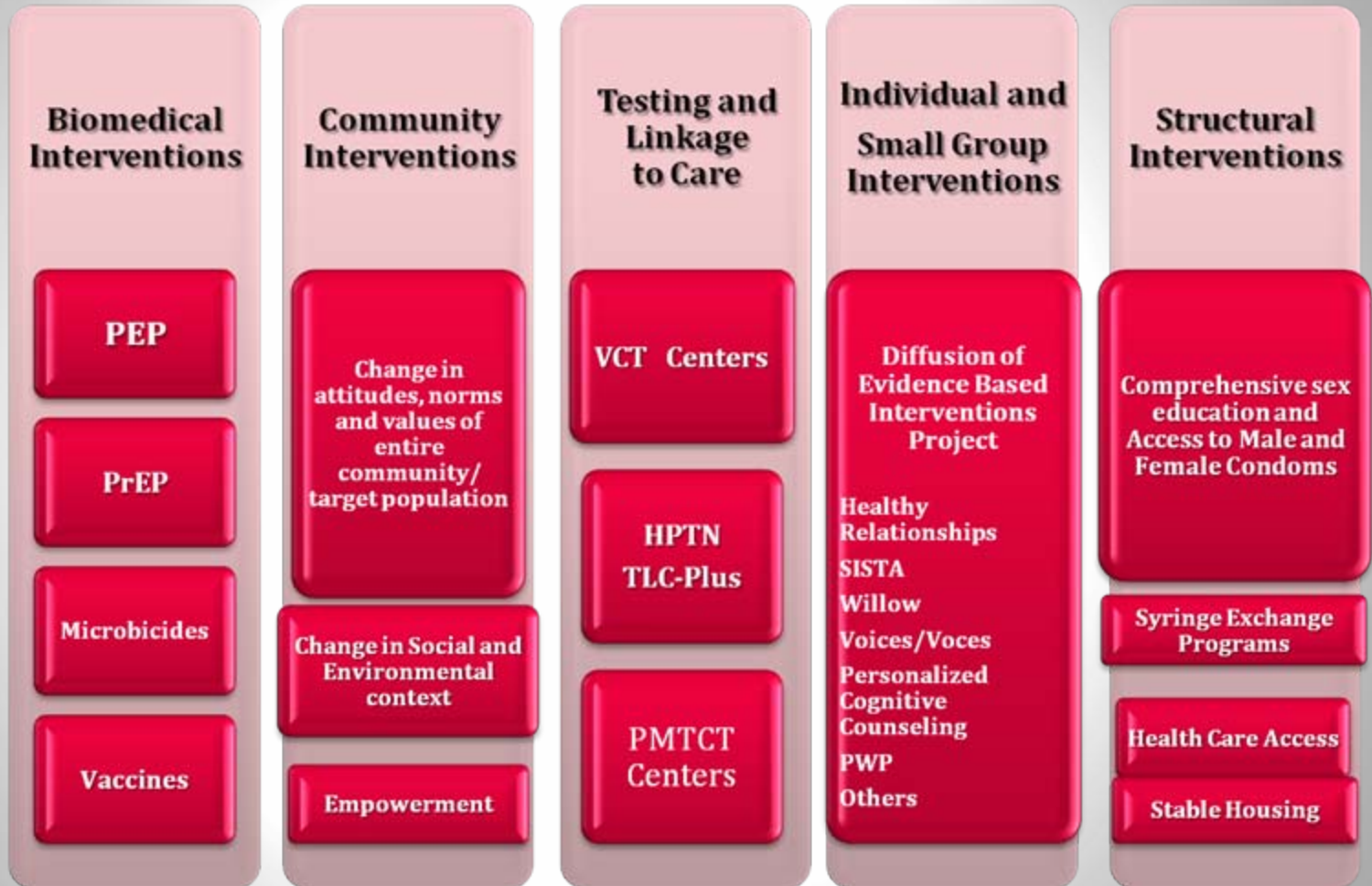
Prevention Science in the US

- 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



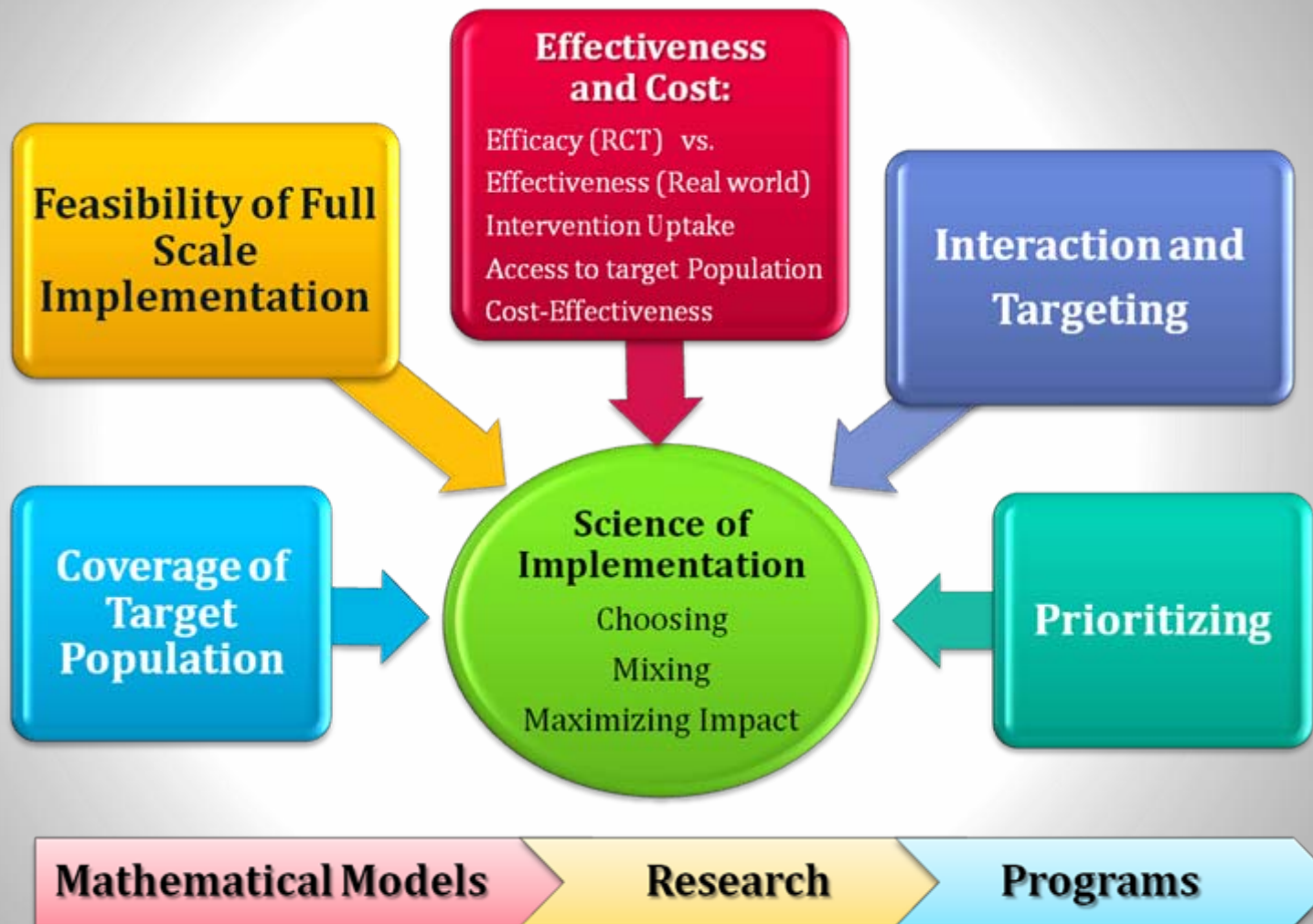
Combination Prevention



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



High Impact Prevention



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

Microbicides

- 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



Linkage to care

- Paucity of data but published evidence shows:
 - 55% of HIV positive are staged &/or enrolled in pre-ART care
 - About $\frac{1}{2}$ of those enrolled in pre-ART care are retained until ART initiation or other endpoint
 - About $\frac{2}{3}$ of those who are in care at ART eligibility initiate treatment
 - *Only $\frac{1}{6}$ - $\frac{1}{3}$ 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



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

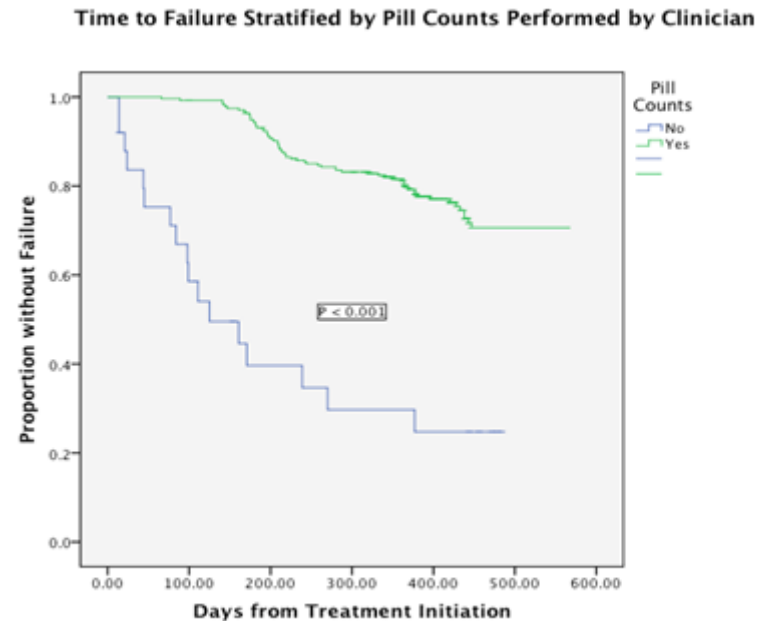


Adherence and Retention in Care

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





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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

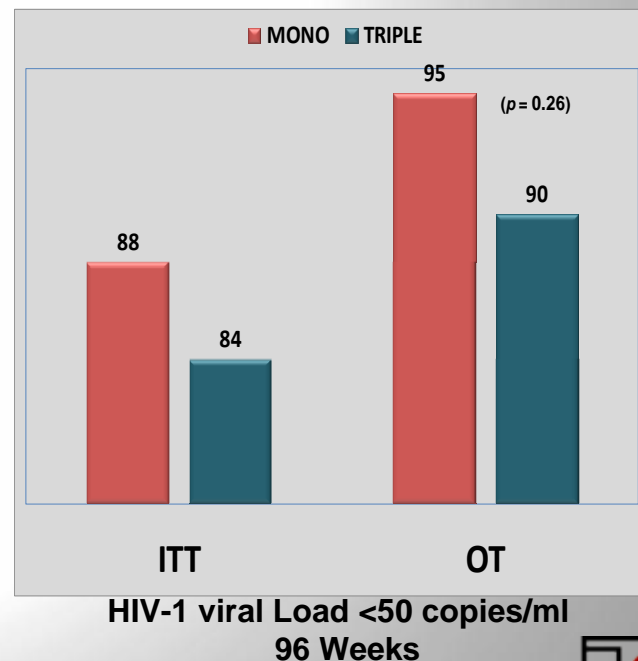
Failures:

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



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

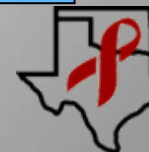
IN resistance 4/23 genotyping samples: N155H (1), N155HN (2), Q148QR and N155HN (1)

No unexpected toxicities occurred

Conclusions: DRV/r + RAL was effective and well tolerated, but those with BL VL >100.000 copies/ml had more VF and Integrase resistance

Virologic Failure (VF) N=112

Period	VF	Never Suppressed	Virologic rebound
Week 24	17 16%	11 65%	6 35%
Week 48	11	0	11 (100%)
Total	28 26%	11	17



Long Term Follow Up of Patients Receiving RAL, ETV, and DRV/r in the ANRS 139 TRIO Trial

ARV experienced
Naïve to RAL, DRV/r and ETV
N=100

RAL 400 BID + DRV/R 600
BID + ETV 200 BID + OBT
(NRTI ± T20)

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

Characteristic	N=100	
Male	89	89%
Age	45	41-51
H/O ARV, (ys)	13	11-15
CD4+ Nadir	80	20-176
CD4+ Wk-0	258	143-351
HIV-1 RNA	4.2	3.6-4.6
Clinical Stage C	41	41





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HAART at 15

What Does the future Hold?

Patrick Yeni, MD
Hospital Bichat Claude Bernard
University Paris
France



15 years of HAART

- 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?

SHORT-TERM

New ARV drugs from existing classes
New co-formulation
Alternative strategies for ARV therapy

MID-TERM

New ARV drugs from new classes
Complementary, non ARV-containing therapy

LONG-TERM

Active and safe drugs to target latent latently infected resting memory CD4 T cells (anti-latency approach)
Active and safe therapy, derived or not from gene therapy to prevent or silence HIV infection of T cells



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-Co A Inhibitors (statins)
- **Inhibition of the Tox Pathway**
- **Others**: Telomerase- based, anti-fibrosis



Some ARV agents in active phase I/II development

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

Yenni; Session 20; Symposium; 18th CROI 2011; Boston, MA



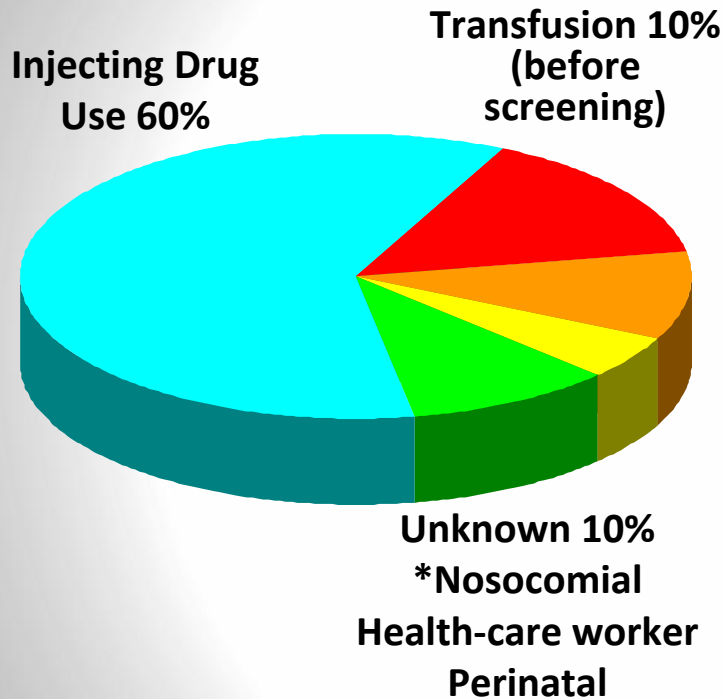


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HEPATITIS C

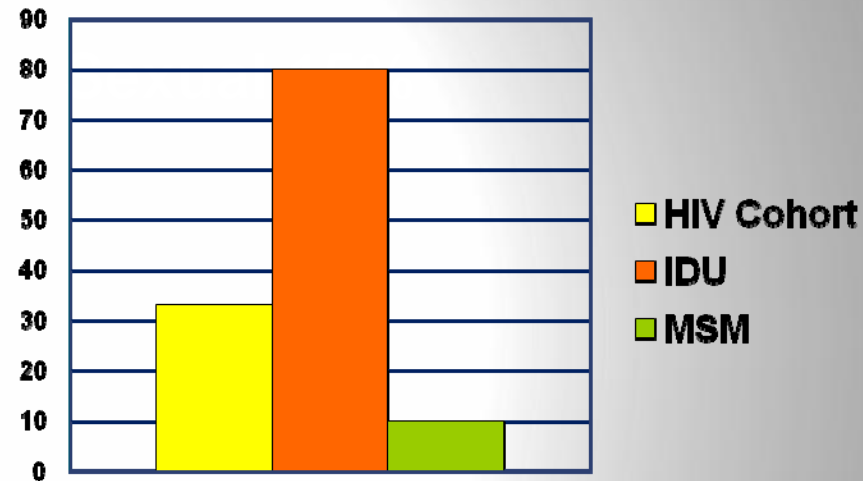


Sources of Infection for Persons with Hepatitis C



Source: Centers for Disease Control and Prevention

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

Alter et al. N Engl J Med 1999

Waldrep et al. Pharmacotherapy 2000

Staples et al. CID, 1999

Chamot et al. AIDS, 1990

Bodsworth et al. Genitourinary Med, 1996



HCV/HIV Treatment:

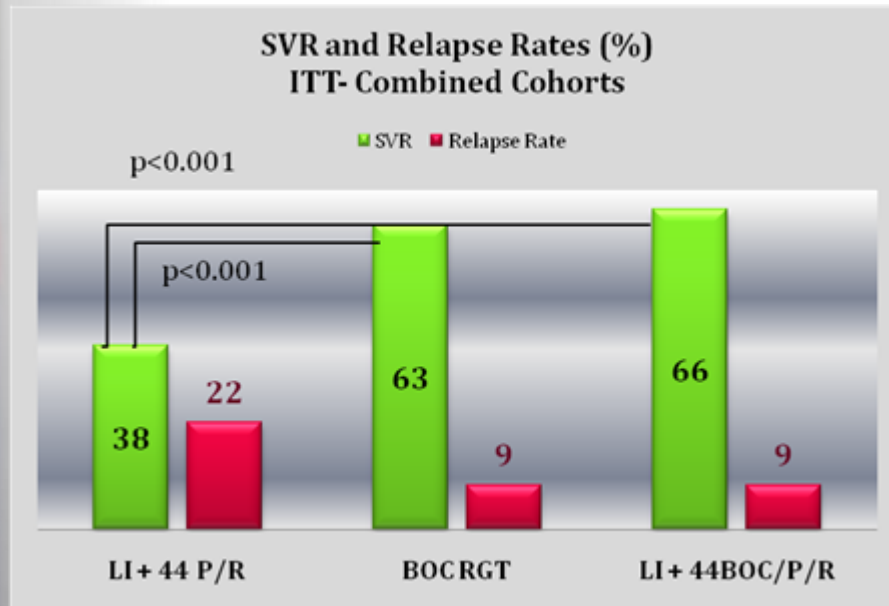
Who should be considered for treatment?

- **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



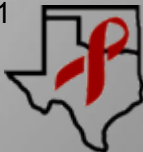
Boceprivir (BOC) + P/R for Treatment-naïve HIV/HCV Coinfected Patients with HCV Genotype-1: SPRINT-2

- **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 Re-treated with BOC + PEGINTRON/RBV

NAME	CLASS	RESPONSE RATE	RECOMMENDED REGIMEN	LENGTH OF TREATMENT	SPECIAL CONSIDERATIONS
Boceprevir	HCV Protease Inhibitor	67% SVR Arm3 59% SVR Arm 2 21% SVR Arm 1	BOC/P/R Arm 3	48 week	Genotype 1 P/R treatment failure patients

Arm 1= (control) P 1.5microg/kg +R 600 to 1400 mg/day x48 week

Arm 2= P/R 4 Week then P/R+800mg BOC 3X/day for 32Week+/- P/R 12 Week

Arm3= P/R 4 Week then P/R+800 BOC 3 X/DAY for 44 week

P=Pegylated Interferon Alpha-2

R=Ribavirin

BOC=Boceprevir

SVR=Sustained virological response

Gordon ; Poster#116, 18th CROI 2011



Novel HCV therapies

Drug	Class	Drug-drug Interactions	Metabolism and Clearance	Regimen
Boceprevir	HCV Protease Inhibitor	EFV ↓ level Ketoconazole ↑ exposure	Hepatic mediated Reversible CYP3A4 inhibitor	Boceprevir+ Pegylated Interferon Alpha+ Ribavirin
Telaprevir	HCV Protease inhibitor	EFV ↓ level by 47% RTV -boosted PI s ↑exposure	Substrate and inhibitor of CYP3A	In combination with Pegylated Interferon and Ribavirin



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.





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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



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

	Sensitivity	Specificity
1 sputum	92.2 %	99.2%
3 sputa	97.6%	98.1%



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

