UPDATE FROM THE CONFERENCE ON RETROVIRUSES AND OPPORTUNISTIC INFECTIONS
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Curriculum Development Group
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Mathematical Models of HIV Transmission

- Low infectivity: \( \sim 0.001 \) per heterosexual encounter
  - \( \sim 10 \) fold variability from person to person
- Slow rate: Doubling time 1-3 years
- Long duration: 5-15 years
- Reduction in Transmission rate by 7 fold would eliminate HIV infection
- HAART has the potential to decrease by 10 fold with good compliance

Williams, #2010
Strategies to Eliminate Transmission

- **Test and treat**
  - ARV within one year from diagnosis
  - Women 20-35
  - Men 25-40
  - Test couples
    - Address barriers
    - Focus on the affected couples

- **PreP for young people**
  - Women 15-20
  - Men 20-25
  - Discordant couples

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Unprotected Sex in Couples

- 84% Spouses
- 13% Steady
- 3% Casual

HIV prevalence in Khutsong, South Africa, 1998

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B Williams, R Bunell; # 2010
San Francisco established aggressive linkages to care from testing facilities.

All patients have viral load testing on HIV diagnosis.

Linkage to care has been associated with:

- Decreased HIV Incidence
- New HIV Diagnosis
- Average HIV Viral Load in the community

Das-Douglas et al. Oral Abstract 33
Superinfection with MDR Virus

Gay man having unprotected sex for two years with a single partner.

He became super-infected with his partners virus.

His viral load increased and his virus showed mutations to the drugs to which his partners virus was resistant.
RV 144 Update: Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

- Community-based, randomized, multicenter, double blind, placebo-controlled efficacy trial in Thai heterosexual population.

- Vaccine strategy: 4 priming injections of ALVAC or placebo and 2 booster injections with AIDSVAX or placebo during first 6 months of the study.

- Patients monitored for HIV-1 infection and early HIV-1 viremia every 6 months for 3 years.

- 3 analyses performed: intention-to-treat, per protocol, and modified intention-to-treat.

Nelson, Oral abstract 74.
All analysis showed decreased infections in the vaccinated group.
Phase 3 Trials of Vicriviroc (VCV) in Treatment-experienced Subjects

Pooled Analysis: VICTOR-E3 & VICTOR-E4

- Pooled analysis of phase III VICTOR-E3 and VICTOR-E4 trials evaluated safety and efficacy of VCV + OBR with PI/rtv compared with OBR alone in treatment-experienced HIV-infected patients.
- Pooled mITT population 721 treated CCR5 HIV (by Trofile ES®)
- Eligibility:
  - HIV-infected with CCR5-tropic HIV-1 only
  - HIV-1 RNA > 1000 copies/mL
  - Documented resistance to agents from ≥ 2 classes (NRTI, NNRTI, or PI)

Baseline characteristics:
Mean age 43, 29% females, 40% non-white,
Mean HIV RNA 4.6 log_{10} copies
Mean CD4 count 257 cells/μL

Gathe J, Abstr. 54 LB.
Pooled VICTOR-E3 and E4: Safe but Not Superior over Potent OBR Alone

- No significant differences between VCV and OBR (p=0.6)

- Subgroup analysis if ≤ 2 active drugs in OBT VCV efficacy (p=0.02)

- Post-hoc analysis showed that use of RAL and DRV in OBT strongly influenced outcome
Integrase Inh. (INI) S/GSK1349572

- One daily dosing,
- No cross resistance to other integrase inhibitors
- 2.5 log ↓ VL after 10 days of mono-therapy
- Two Phase IIB in progress in treatment naive and experienced

Change in Viral Load with Dose

Johns B, #55.
ODIN Trial: 48 Weeks Once vs. Twice Daily DRV/r in treatment-experienced with No DRV RAM

- Twice-daily DRV/RTV 600/100 mg approved for ARV experienced
- Once-daily DRV/RTV 800/100 mg approved for ARV naive
- Eligibility:
  - HIV-1 RNA > 1000 copies/mL
  - CD4 > 50 cell/mm3
  - No DRV RAMS: V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, L89V
  - No previous or current use of enfuvirtide, tipranavir, or darunavir
- Primary endpoints:
  - HIV-1 RNA < 50 copies/mL at Week 48

Baseline characteristics:
Mean age 40, 27% females, 65% non-white
Mean HIV RNA 4.16 log_{10} copies
Mean CD4 count 228 cells/μL

Cahn P, et. al; # 57.
Single-tablet, fixed dose Regimen (QUAD) 24 weeks results

QUAD (Cobicistat): Elvitegravir/Emtricitabine/Tenofovir/GS-9350

ARV-naïve
CD₄ ≥ 50
HIV-1 RNA ≥5,000
NO
NRTI, NNRTI, or PI resistance

Study 236 (n=71)
GS-9350/EVG/FTC/TDF
EFV/FTC/TDF
GS-9350/ATV/FTC/TDF
RTV/ATV/FTC/TDF

Study 216 (n=79)

Cohen C, Abstr. #
58 LB
### QUAD (Cobicistat)

<table>
<thead>
<tr>
<th>Week 24 Outcome</th>
<th>QUAD (48 pts)</th>
<th>ATRIPLA (23 pts)</th>
<th>GS-9350/ATV + TRUVADA (50 pts)</th>
<th>RTV/ATV+ TRUVADA (29 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT analysis HIV-1 RNA &lt;50</td>
<td>90%</td>
<td>83%</td>
<td>84%</td>
<td>86%</td>
</tr>
<tr>
<td>Median CD4 Increase from BL</td>
<td>123</td>
<td>124</td>
<td>206</td>
<td>190</td>
</tr>
<tr>
<td>Treatment Related AE (any grade)</td>
<td>17 (35%)</td>
<td>13 (57%)</td>
<td>10 (20%)</td>
<td>7 (24%)</td>
</tr>
<tr>
<td>Study Discontinuations</td>
<td>6%</td>
<td>13%</td>
<td>8%</td>
<td>10%</td>
</tr>
</tbody>
</table>

- Cobicistat-boosted non-inferior to Atripla (VL< 50 c/mL at Wk 24)
- Cobicistat-boosted ATV similar to rtv-boosted ATV (VL < 50 c/mL at Wk 24)
- Similar CD4+ cell count increases in both arms of each study

Cohen C; # 58LB.
**ACTG 5202: Study Design**

- Stratified by screening HIV-1 RNA
  - \( \geq 1000 \text{ c/mL} \)
  - \( < \text{ or } \geq 100,000 \text{ c/mL} \)
- Any CD4+ count \( > 16 \) years of age
- ART naïve
- 1857 Enrolled
- Randomized 1:1:1:1

- Enrolled 2005-2007
- Followed through Sept 2009, 96 wks after last pt enrolled

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**Tox**

- Arm A:
  - TDF/FTC QD
  - ABC/3TC Placebo QD
  - EFV QD

- Arm B:
  - ABC/3TC QD
  - TDF/FTC Placebo QD
  - EFV QD

- Arm C:
  - TDF/FTC QD
  - ABC/3TC Placebo QD
  - ATV/r QD

- Arm D:
  - ABC/3TC QD
  - TDF/FTC Placebo QD
  - ATV/r QD

Daar E, et al. Oral 59LB.
ACTG 5202 Time to Virologic Failure (End of Study: Low Viral Load Stratum)

ABC/3TC versus TDF/FTC with:

ATV/r: HR 1.26 (95% CI 0.76, 2.05)
Prob. VF free at wk 96: 88.3 vs. 90.3%, diff -2.0% (95% CI -7.5, 3.4)

EFV: HR 1.23 (95% CI 0.77, 1.96);
Prob. VF free at wk 96: 87.4 vs. 89.2%, diff -1.8% (95% CI -7.5, 3.9)
HIV AND CO-INFECTIONS
High Prevalence of Asymptomatic STI’s in HIV-Positive MSM, Visiting HIV Outpatient Clinics

<table>
<thead>
<tr>
<th>STD</th>
<th>LOCATION</th>
<th>TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. tracomatis</td>
<td>Oral swabs, anal self swabs, urine</td>
<td>PCR</td>
</tr>
<tr>
<td>N. gonorrhea</td>
<td>Oral swabs, anal self swabs, urine</td>
<td>PCR</td>
</tr>
<tr>
<td>HBV</td>
<td>serum</td>
<td>ABs</td>
</tr>
<tr>
<td>HCV</td>
<td>serum</td>
<td>ABs</td>
</tr>
<tr>
<td>T. pallidum</td>
<td>serum</td>
<td>RPR</td>
</tr>
</tbody>
</table>

- 659 MSM (median age 45.4)
  - HIV outpatient clinic of 2 academic hospitals
  - STI screening during a routine visit
- Patients spontaneously reporting STI symptoms were excluded
- MSM completed questionnaire about sexual behaviour previous 6 months.

Heiligenberg M; Poster #1022.
High Prevalence of Asymptomatic Sexually Transmitted Infections in HIV-Positive MSM, Visiting HIV Outpatient Clinics in the Netherlands

<table>
<thead>
<tr>
<th></th>
<th># (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis</td>
<td></td>
</tr>
<tr>
<td>Known/treated syphilis</td>
<td>204/658 (31.0)</td>
</tr>
<tr>
<td>Newly detected early or late syphilis</td>
<td>33/658 (5.0)</td>
</tr>
<tr>
<td>Hepatitis B (HBV)</td>
<td></td>
</tr>
<tr>
<td>Known (acute or chronic) HBV infection</td>
<td>39/650 (6.0)</td>
</tr>
<tr>
<td>Susceptible</td>
<td>91/650 (14.0)</td>
</tr>
<tr>
<td>Newly detected HBV infection</td>
<td>1/650 (0.5)</td>
</tr>
<tr>
<td>Hepatitis C (HCV)</td>
<td></td>
</tr>
<tr>
<td>Known HCV Infection</td>
<td>27/649 (4.2)</td>
</tr>
<tr>
<td>Newly detected HCV infection</td>
<td>3/649 (0.5)</td>
</tr>
<tr>
<td>Chlamydia</td>
<td></td>
</tr>
<tr>
<td>Anal</td>
<td>48/637 (7.5)</td>
</tr>
<tr>
<td>Urethral</td>
<td>9/626 (1.4)</td>
</tr>
<tr>
<td>Total</td>
<td>56/655 (8.6)</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td></td>
</tr>
<tr>
<td>Anal</td>
<td>20/637 (3.1)</td>
</tr>
<tr>
<td>Urethral</td>
<td>2/624 (0.3)</td>
</tr>
<tr>
<td>Total</td>
<td>22/655 (3.4)</td>
</tr>
</tbody>
</table>

More than 17% of HIV+ MSM attending HIV outpatient clinics in the Netherlands, had one or more asymptomatic STI, mostly CT and syphilis.

Having had more than 2 steady or more than 2 casual partners, unsafe anal sex or other high-risk sexual techniques, and enema use were associated with the presence of asymptomatic STD.

Routine (bi-) annual screening for anal STI and syphilis, in HIV+ MSM reporting any of the factors associated with STI in this study, might be considered to prevent the further spread of STI.
Vaccine Non-Responders had Shorter Time to Development of Cancer \(^{759}\)
- Vaccine response rate in those with cancer vs cancer-free: 37% vs 60.7% \((p=0.015)\)

Vaccine Non-Responders had increased AIDS or Death \(^{625}\)
- 7-year incidence of AIDS or death: 25% vs 9% \((p<0.001)\)
- Adj.HR 0.56, 95% CI 0.33-0.96

Vaccination Schedule
- Accelerated
  - Standard dose at T0,1 and 3 wks
  - Non-inferior efficacy only for those with CD4 >500

- Alternate 4-part high dose
  - Double dose at T0,4,8 & 24 wks
  - Better response than standard 3 dose series, especially:
    - Older age
    - VL >50
    - Males
    - CD4 <350
Clinical Features of Subjects Infected with HIV and H1N1 Influenza Virus

- Time from onset to hospitalization inversely related to CD4 counts and directly related to length of stay and death.

- Oseltamivir treatment was delayed in some patients with OI because the OI masked symptoms associated with H1N1 infection.
  - Higher death rates for those with OIs.

- During an outbreak “…AIDS patients with respiratory symptoms should all be screened for influenza or consideration should be given to empirically starting antiviral treatment if tests are not available or could be delayed.”

Ormbsy C, et.al. #803 LB
120 participants received a single dose of licensed, unadjuvanted H1N1 vaccine (Novartis, 2009).

Seroconversion was defined as an anti-hemagglutinin Ab titer > 1:40 at 3 weeks.

Overall 69% had titers > 1:40 at 3 weeks, but 25% of patients had baseline titers > 1:40.

In the 89 patients with baseline titers < 1:40, 61% had a response > 1:40 at 3 weeks.

Conclusion: “… a modified vaccine schedule or adjuvanted vaccine should be considered for patients with immunosuppression due to HIV.”

Tebas P. et. al; 806LB.
## Risk Factors Associated with Renal Impairment: Cohort Analysis

<table>
<thead>
<tr>
<th>Cohort</th>
<th>N</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swiss HIV Cohort</td>
<td>2253</td>
<td>TDF, Increasing Age, Female Gender</td>
</tr>
<tr>
<td>French ANRS Aquitaine</td>
<td>2613</td>
<td>TDF, Increasing Age, Female Gender, CE4 &lt; 200</td>
</tr>
<tr>
<td>US ART Naive</td>
<td>4588</td>
<td>Prior CKD</td>
</tr>
<tr>
<td>D:A:D</td>
<td>30,000 pt/ys</td>
<td>TDF</td>
</tr>
</tbody>
</table>
Risk Factors Associated with Renal Impairment: ACTG 5202 at 96 weeks

Change in CrCL

-2 0 2 4 6 8 10

EFV  ATZ/r

P < 0.001 for ATZ/r + TDF vs other regimens

ABC/3TC

TDF/FTC
NRTIs and Risk of MI: Recent* and Cumulative Exposure

<table>
<thead>
<tr>
<th>D:A:D</th>
<th>ZDV</th>
<th>ddI</th>
<th>ddC</th>
<th>d4T</th>
<th>3TC</th>
<th>ABC</th>
<th>ABC</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR 95% CI</td>
<td></td>
<td></td>
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<tr>
<td>RR per year</td>
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<tr>
<td>95% CI</td>
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<tr>
<td>#PYFU:</td>
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<td></td>
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<tr>
<td>#MI:</td>
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</tr>
</tbody>
</table>

* Recent use defined as still using or stopped within last 6 months.
** Not shown (low number of patient currently on ddC)

Lundgren J, 44LB
Longitudinal Progression of Bone Mineral Density Loss

- **New York Cohort**
  - **Baseline DEXA**
    - 95 (42%) normal
    - 7.2 per 100 PY osteopenia incidence
  - DEXA After 2 Years
    - 18 (19%) osteopenia
    - 29 (16%) osteoporosis
    - 25 (76%) still osteoporosis

- **French Cohort**
  - **Baseline DEXA**
    - 72 (28%) normal
    - 183 (72%) osteopenia
    - 9.57 per 1000PY incidence osteoporosis
  - DEXA After 2 Years
    - 20 (28%) osteopenia
    - 29 (16%) osteoporosis

Sharma A, et al. #746; Cazanave C et al. #747
## Vitamin D

### Normal Functions\(^{753}\):
- Calcium homeostasis & bone metabolism
- Antineoplastic & anti-inflammatory processes
- Immunity – involved in:
  - Induction of antimicrobial peptide that kills MTB & others
  - Macrophage phagocytosis, monocyte H\(_2\)O\(_2\) secretion, neutrophil motility

### Possible Deficiency-Related Complications \(^{751, 753}\):
- Diabetes, CVD, renal disease
- HIV-wasting, anemia, maternal disease progression

<table>
<thead>
<tr>
<th></th>
<th>Normal Metabolism</th>
<th>Altered Metabolism (^{750})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vit D</td>
<td>Produced in skin from sun exposure Absorbed from food consumed</td>
<td>- Sun block, melanin, cloudy weather - Insufficient intake</td>
</tr>
<tr>
<td>25 (OH)D</td>
<td>Hydroxylated in liver</td>
<td>- EFV induces P450 conversion to inactive calcitronic acid</td>
</tr>
<tr>
<td>1,25 (OH)D</td>
<td>(\alpha)-Hydroxylated in kidneys</td>
<td>- RTV inhibition of (\alpha)-OH - Renal insufficiency - EFV induces P450 conversion to inactive calcitronic acid</td>
</tr>
</tbody>
</table>

Dao C, et al. #750; Mehta S, et al. #753
Vitamin D Deficiency in HIV

- **Higher Rates During Cloudy Season**
  - Switzerland: 42-52% vs 14-18% \(^{752}\)
  - Italy: 43% vs 9%, adjOR 8.3 (p 0.0001) \(^{751}\)

- **Other Factors Associated with Deficiency** \(^{751}\)
  - Older age, non-caucasian race, lower BMI, lower CD4, prior exposure to NNRTI

- **Not Associated with TDF-Related BMD Loss** \(^{749}\)
  - 25(OH)D deficiency not correlated with TDF use
  - Hyper-PTH correlated with GFR <60 and prior AIDS but not with TDF use

Wirz S #749; Borderi M #751; Müller N #752.
Pregnancy Outcomes with Non-AZT Containing regimens

- European cohort: 26 centers in 10 European countries.

- 7353 pregnancies on HAART between 2008-2009
  - 6374 on AZT-HAART
  - 1199 on non-AZT-HAART

- No difference in risk of:
  - Detectable VL at delivery.
  - Congenital abnormality.
  - MTCT.

Tariq S, et.al. #895
CSF Viral Loads

- **Plasma viral load**: strongest correlate of CSF viral load → importance of systemic HIV suppression for control of HIV in the nervous system.

- **Without ART**: higher CSF viral loads correlate with older age + more advanced current and past immune suppression.

- **With ART**: detectable CSF viral loads associated with worse adherence & worse estimated antiretroviral penetration & non-white ethnicity.

- Both correlated with longer duration of HIV + more advanced HIV disease.

- Non-white ethnicity also associated with HCV co-infection.

- **Without ART**, the 13% that had CSF viral loads that were at least as high as plasma viral loads had worse global neurocognitive performance.

- Explanation for why the relative rather than the absolute value of CSF viral loads was associated with outcome remains to be determined.

Letendre S., et.al. #172
Correlates of CSF Viral Loads: The Charter Cohort
1221 volunteers

<table>
<thead>
<tr>
<th>CNS Penetration-Effectiveness Ranks 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs</strong></td>
</tr>
<tr>
<td>4 Zidovudine</td>
</tr>
<tr>
<td>3 Abacavir <em>Emtricitabine</em></td>
</tr>
<tr>
<td>2 Didanosine Lamivudine Stavudine</td>
</tr>
<tr>
<td>1 Tenofovir Zalcitabine</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
</tr>
<tr>
<td><em>Nevirapine</em></td>
</tr>
<tr>
<td>Delavirdine <em>Efavirenz</em></td>
</tr>
<tr>
<td><em>Etravirine</em></td>
</tr>
<tr>
<td><strong>PIs</strong></td>
</tr>
<tr>
<td><em>Indinavir-r</em></td>
</tr>
<tr>
<td><em>Darunavir-r</em></td>
</tr>
<tr>
<td><em>Fosamprenavir-r</em></td>
</tr>
<tr>
<td><em>Indinavir</em></td>
</tr>
<tr>
<td><em>Lopinavir-r</em></td>
</tr>
<tr>
<td><em>Atazanavir</em></td>
</tr>
<tr>
<td><em>Atazanavir-r</em></td>
</tr>
<tr>
<td><em>Fosamprenavir</em></td>
</tr>
<tr>
<td><em>Nelfinavir</em></td>
</tr>
<tr>
<td><em>Ritonavir</em></td>
</tr>
<tr>
<td><em>Saquinavir</em></td>
</tr>
<tr>
<td><em>Saquinavir-r</em></td>
</tr>
<tr>
<td><em>Tipranavir-r</em></td>
</tr>
<tr>
<td><strong>Entry/Fusion Inhibitors</strong></td>
</tr>
<tr>
<td>Maraviroc</td>
</tr>
<tr>
<td><strong>Integrase Inhibitors</strong></td>
</tr>
<tr>
<td>Raltegravir</td>
</tr>
</tbody>
</table>

Letendre S, et. al. #172
WOMEN AND CHILDREN
Contraception in HIV
Effective Contraception Use Among Women

- Surgical Sterilization: 13.5%, 13.4%, 4.1%
- IUD/Subdermal Implants: 1.9%, 7.1%, 6.5%
- Oral Contraceptive/Patch/Ring/Injectable: 9.3%, 17.1%, 32.9%

Horberg M, et. al; #932; Mwachari C, et. al; #933; Cu-Uvin S, et. al; #934
Contraception in HIV
Effective Contraception Use Among Women

- HIV+ women contraception:
  - Effective reversible contraception less utilized (all forms) than healthy or women with other chronic medical conditions (OCMC)
  - Less effective methods more commonly utilized (condoms only or abstinence)

- Use of levonorgestrel IUD
  - No increase on viral shedding, inflammatory cytokines or STIs
  - Effective, acceptable, tolerable

- Emergency contraception with Levonorgestrel and EFV
  - Lower mean AUC (58%), Cmax (45%) and Cmin (69%)

Horberg M, et. al; #932; Mwachari C, et. al; #933; Cu-Uvin S, et. al; #934
ARV in Children

- 3 Pediatric formulations of RAL
- Qday Elvitegravir + Pir safe and tolerated in adolescents
- Few DRV RAM noted in children
- >180 weeks sustained virologic response with FPV/r in naïve and experienced perinatally infected children
- RTV but not LPV had significant increase in Total Cholesterol
- DO NOT CRUSH LPV/r
  - Decrease by 40%

Braynard K, et. al; #872; Gaur A, et. al; #874; Boyd, K; et. al; #851; Palladino C, et. al; #876; Rhakhmanina N, et. al; #867; Diep H, et. al; #877;
Rates of Sexual and Perinatal HIV Transmission According to Viral Load

HIV Viral Load, RNA Copies/mL

Heterosexual Discordant Couple Transmission

- <400
- 400-3499
- 3500-9999
- 10,000-49,999
- >50,000

Transmission Rate/100 Person Years

Transmission Rate% of Mothers

Perinatal Transmission

- <400
- 400-3499
- 3500-9999
- 10,000-29,999
- >30,000

Sources: Quinn et al., NEJM, 2000; Cooper et al., JAIDS, 2002
Pregnancy Outcomes with Non-AZT Containing regimens

- **European cohort**
  - 2008-2009
  - 26 centers in 10 European countries
  - 7353 pregnancies on HAART
    - 6374 on AZT-HAART
    - 1199 on non-AZT-HAART

- **No difference in risk of**
  - Detectable VL @ delivery
  - Congenital abnormality
  - MTCT

Tariq S, et. al; Poster 895.
FUTURE DIRECTIONS
Our Common Goal:

“Controlling and Ultimately Ending the HIV/AIDS Pandemic”
“High Risk- High Impact Strategies”
Anthony Fauci
NIAID, NIH Director
Why and How?

- **Aggressively “seek, test and treat”**
  - Improved survival time from 26 weeks to 3-5 decades
  - Test and treat: Lowering Community VL

- **Cure existing infections**
  - Current treatment paradigm is not enough and not sustainable
  - Sterilizing vs. Functional

- **Prevent new infections**
  - Access to research proven modalities
  - Microbicides and PrEP
  - Vaccines
Understanding The Host

- Chronic immune activation can be attributed to microbial translocation
  - High Mobility Group Box Protein (HMGB1)
    - Marker of tissue necrosis and immune activation
  - Lipopolysaccharide (LPS)
    - Marker of bacterial translocation
  - Both plasma levels elevated before treatment
  - VL was 74% higher in those with elevated HMGB1 and LPS above median
  - After 2 years of ART
    - LPS reduced to the same median as control
    - HMGB1 reduced but not normalized

Troseid M, et.al; Poster ***