Advances in Antiretroviral Therapy

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2015 Chinese HIV Research Conference
Shanghai, China
Outline

• Background of ARV
• Importance of HIV viral suppression
• Second Line Treatment
• Future treatment Strategies
Potential Therapeutic Targets

- CCR5
- Fusion Inhibitors
- Reverse Transcriptase Inhibitors
- Integrase Inhibitors
- Protease Inhibitors
Evolution of the Therapeutic Goal Line

• In vivo Antiviral activity (1985-1995)
• Viral suppression (1995-2003)
• Dosing and regimen simplification (2003-2005)
• Long term durability (2005-present)
  – Durable viral suppression
  – Limited chronic toxicity profile
  – Expanded use of morbidity friendly agents
• Broadening indications (2010-2015)
  – Expanded treatment recommendations- treat all HIV infected pts.
  – Treatment as Prevention to include PrEP
• Future (2015-2020)
  – Expanded therapeutic targets – targeting host cell pathways
  – Development of Therapeutic Strategies to decrease pro-viral copy number and reservoir of infection towards “functional cure”
Evolution of the Therapeutic Goal Line: Use of Co-Morbidity Friendly ARVs

• Recognition of HIV as a metabolic disease associated with accelerated aging
  – Accelerated CVD
  – Metabolic disease
  – Increased risk of Cancer
  – Increased rate of Aging

• Leading cause of death for person living with HIV infection
  – Heart disease
  – Cancer
  – Renal Disease
  – Liver Disease
## FDA-Approved Drugs for HIV Therapy 2015

### NRTIs
- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zalcitabine (ddC) *withdrawn 2005*
- Zidovudine (ZDV)
- 3TC/ABC
- 3TC/ABC/ZDV
- 3TC/ZDV
- FTC/TDF

### NNRTIs
- Delavirdine (DLV)
- Efavirenz (EFV)
- Nevirapine (NVP)
- Etravirine
- Rilpivirine

### PIls
- Amprenavir (APV) *discontinued 2004*
- Atazanavir (ATV) and Atazanavir/Cobicstat
- Darunavir (DRV) and Darunavir/Cobicstat
- Fosamprenavir (FPV)
- Indinavir (IDV)
- Lopinavir/ritonavir (LPV/RTV)
- Nelfinavir (NFV)
- Ritonavir (RTV)
- Saquinavir (SQV hgc)
- Tipranavir (TPV)

### NNRTIs
- Delavirdine (DLV)
- Efavirenz (EFV)
- Nevirapine (NVP)
- Etravirine
- Rilpivirine

### Fusion Inhibitors (Fis)
- Enfuvirtide (ENF)

### Integrase Inhibitors
-Raltegravir
-Elvitegravir
-Dolutegravir

### CCR5 antagonist
-Maraviroc

### Multiple Class
- TDF/FTC/EFV
- TDF/FTC/Rilpivirine
- TDF/FTC/Cobicstat/Elvitegravir
- ABC/3TC/Dolutegravir
DHHS Guidelines: Recommended Regimens
Initiate ARV treatment in all patients with HIV infection

Regardless of Baseline HIV RNA Level or CD4 Count

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Efavirenz/emtricitabine/tenofovir DF*</th>
</tr>
</thead>
</table>
| PI          | Atazanavir + ritonavir + emtricitabine/tenofovir DF  
Darunavir + ritonavir (qd) + emtricitabine/tenofovir DF |
| INSTI       | Raltegravir + emtricitabine/tenofovir DF  
Elvitegravir/cobicistat/emtricitabine/tenofovir DF*  
Dolutegravir + abacavir/lamivudine  
Dolutegravir + emtricitabine/tenofovir DF |

*Available as a once-daily, single-tablet regimen.

Notes:
Efavirenz: avoid use in women trying to conceive or are sexually active and not using contraception.
Lamivudine may substitute for emtricitabine or visa versa.
Tenofovir DF: use with caution in patients with renal insufficiency.
Atazanavir + RTV: absorption depends on food and low gastric pH.
Elvitegravir/cobicistat/emtricitabine/tenofovir DF: only for patients with pre-ART creatinine clearance ≥70 mL/min. Abacavir: only for patients who are HLA-B*5701 negative.

## Chinese Free ARV Program: ART initiation criteria

### Evolution when to Start ARV

<table>
<thead>
<tr>
<th>CD4 ≤ 200</th>
<th>CD4 ≤ 350</th>
<th>CD4 ≤ 500</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 1 1 1 1</td>
<td>1 1 1 1 1</td>
<td>1 1 1 1 1</td>
</tr>
<tr>
<td>9 9 9 9 9</td>
<td>9 9 9 9 9</td>
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<tr>
<td>8 8 8 8 8</td>
<td>8 8 8 8 8</td>
<td>8 8 8 8 8</td>
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<tr>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
<td>1 2 3 4 5</td>
</tr>
</tbody>
</table>

(INSTITUTE OF HUMAN VIROLOGY)

(UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE)
China First Line Regimens for Naïve Patient

<table>
<thead>
<tr>
<th>TDF or AZT</th>
<th>+ 3TC</th>
<th>EFV or NVP now</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT or D4t</td>
<td>+ 3TC</td>
<td>NVP or EFV before</td>
</tr>
</tbody>
</table>

- AZT cannot be used when Hb < 90g/L or ANC <0.75×10⁹/L at baseline。
- For HBV co-infected patients, the first choice is TDF/3TC/EFV.
- Consider using ABC when TDF and AZT both cannot be used.
- For pts. who are using D4T, D4T should be changed to TDF or AZT gradually.
Outline

• Background ARV
• Importance of HIV viral suppression
• Second Line Treatment
• Future treatment Strategies
Active HIV Replication: Is it a Good Thing to Let Persist? NO

- Irreversible immune disturbances
- Long term impact of Immune System recovery
- Degree and duration Impacts Initial Treatment Success
- Risk to limit future treatment options
- Increase Metabolic-cardiovascular and small vessel disease risk
- Increase Neoplasm Risk
- Persistent Public Health Risk
Permanent Loss of CD4 if Wait to Start

- CD4-count increases on sustained suppressive (<400 c/mL) ARV treatment (n=655) by baseline count
  - >350 cells/mm³: CD4 counts return to near-normal levels
  - ≤350 cells/mm³: CD4 counts significantly increased but plateau after 4 years below normal range
- Differences in CD4 counts associated with differences in morbidity and mortality


From MS Saag, MD and ES Daar, MD at San Francisco, CA: March 29, 2013, IAS-USA.
CD4+ T-cell Count Associated with Risk of Non-HIV Related Death (D:A:D Study)

- Cohort study of >23,000 patients in Europe, Australia, USA
- 1248 (5.3%) deaths 2000–2004 (1.6/100 person-years)
  - Of these, 82% on ART
- Both HIV- and non-HIV-related mortality associated with CD4+ cell count depletion, suggesting role for immunosuppression in causes of death typically considered not HIV-related*

*Liver-related: Chronic viral hepatitis, liver failure (other); malignancy-related: malignancy, non-AIDS non-hepatitis; heart-related: MI, other CVD, other heart disease
Association of non-Hodgkin's Lymphoma and Duration of HIV suppression AIDS: 2009, 23:2301-2308

(a) Distribution by duration of ARV treatment

(b) Duration of cART (months)

Duration of HIV suppression (months)
Evolution of the Therapeutic Goal Line Continues: Epidemic Control

Treatment as Prevention

- Treating discordant partners to reduce infectivity
- Broadening treatment to all HIV infected individuals to reduce infectivity and reduce Community Viral Load
- Pre-exposure prophylaxis for high risk individuals
HPTN 052: HIV Prevention in Stable Heterosexual Couples

- DSMB halts trial after a median follow-up: 1.7 years
  - HIV RNA <400 copies/mL
    - Early ART: 90%
    - Delayed ART: 93%
- Linked HIV transmission to HIV-negative partner (n=28)
  - Early therapy (n=1)
    - 0.1 per 100 person-years
  - Delayed therapy (n=27)
- Early ART led to a 96% reduction of sexual transmission of HIV in serodiscordant couples

Cumulative Probability

Years

HR: 0.04
(95% CI 0.01-0.27)
(P<0.001)

0 1 2 3 4 5

Early ART

Delayed ART

0 0.05 0.1 0.15 0.2

Cumulative Probability
START: Immediate vs Deferred Therapy for Asymptomatic, ART-Naive Pts

- International, randomized trial

HIV-positive, ART-naive adults with CD4+ cell count > 500 cells/mm$^3$ (N = 4685)

- Composite primary endpoint: any serious AIDS-related (AIDS-related death or AIDS-defining event) or non-AIDS–related event (non-AIDS–related death, CVD, end-stage renal disease, decompensated liver disease, non-AIDS–defining cancer)

- Mean follow-up: 3 yrs; median baseline CD4+ cell count: 651 cells/mm$^3$; median baseline HIV-1 RNA: 12,759 copies/mL

- Median CD4+ cell count at initiation of ART for deferred group: 408 cells/mm$^3$

**Immediate ART**
ART initiated immediately following randomization
(n = 2326)

**Deferred ART**
Deferred until CD4+ cell count ≤ 350 cells/mm$^3$, AIDS, or event requiring ART
(n = 2359)

Study closed by DSMB following interim analysis

START: 57% Reduced Risk of Serious Events or Death With Immediate ART

- 4.1% vs 1.8% in deferred vs immediate arms experienced serious AIDS or non-AIDS–related event or death (HR: 0.43; 95% CI: 0.30-0.62; \( P < .001 \))

Reproduced with permission.
## START: Primary Endpoint Components With Immediate vs Deferred ART

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Immediate ART (n = 2326)</th>
<th>Deferred ART (n = 2359)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Rate/100 PY</td>
<td>N</td>
<td>Rate/100 PY</td>
</tr>
<tr>
<td>Serious AIDS-related event</td>
<td>14</td>
<td>0.20</td>
<td>50</td>
<td>0.72</td>
</tr>
<tr>
<td>Serious non-AIDS–related event</td>
<td>29</td>
<td>0.42</td>
<td>47</td>
<td>0.67</td>
</tr>
<tr>
<td>All-cause death</td>
<td>12</td>
<td>0.17</td>
<td>21</td>
<td>0.30</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>6</td>
<td>0.09</td>
<td>20</td>
<td>0.28</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>1</td>
<td>0.01</td>
<td>11</td>
<td>0.16</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>3</td>
<td>0.04</td>
<td>10</td>
<td>0.14</td>
</tr>
<tr>
<td>Non-AIDS–defining cancer</td>
<td>9</td>
<td>0.13</td>
<td>18</td>
<td>0.26</td>
</tr>
<tr>
<td>CVD</td>
<td>12</td>
<td>0.17</td>
<td>14</td>
<td>0.20</td>
</tr>
</tbody>
</table>

START: Cancer Events With Immediate vs Deferred ART

<table>
<thead>
<tr>
<th>Cancer Event, n</th>
<th>Immediate ART (n = 2326)</th>
<th>Deferred ART (n = 2359)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>14</td>
<td>39</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Lymphoma, NHL + HL</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cervical or testis cancer</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other types*</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>

Cumulative % With Event

Time to Cancer Event

Rate/100 PY: immediate, 0.20; deferred, 0.56 (HR: 0.36; 95% CI: 0.19-0.66; P = .001)


NEW WHO HIV ARV TREATMENT GUIDELINES  2015

- Initiate ARV treatment for all patients with HIV infection, regardless of WHO clinical stage and at any CD4 count
It is very simple to make HIV care and treatment complicated. It is a little more complicated, at first, to keep HIV care and treatment simple.

Begin with the end in mind.

Durability of the Initial Regimen is the Key to Sustainability, Scalability, and Long Term ARV Access in Global HIV Treatment Programs
Durability of Initial Regimen: Key Factors

• Regimen Choice
• Care Delivery System
  – Role of enhanced treatment preparation and treatment support, especially during induction of viral control
• Treatment Strategy
Time to Switch to 2\textsuperscript{nd} line Regimen

PLO AIDSRelief: 2008

- D4T/3TC/EFV
- Truvada/NVP or EFV

Months:
0 3 6 9 12 15 18 21 24 27 30 33 36

Probability:
0.00 0.25 0.50 0.75 1.00

Legend:
- D4T/3TC/NVP
- D4T/3TC/EFV
- AZT/3TC/NVP
- AZT/3TC/EFV
- TRUVADA/NVP
- TRUVADA/EFV

Truvada/NVP or EFV
Durability of Initial Regimen: Key Factors

- Regimen Choice
- Care Delivery System
  - Role of enhanced treatment preparation and treatment support especially during induction of viral control
- Treatment Strategy
Retrospective review of patients enrolled in the AIDSRelief program treatment sites between Aug 2004-June 2005. Loss to follow up (ltfu) data was aggregated from the quarterly grant reports.

Loss to follow up data is cumulative over time for each program in each country, and programs are tiered according to their particular components.

**Tier I**
Adherence Counseling only
Prior to Starting ART

**Tier II**
Adherence counseling *plus* a structured treatment preparation plan*

**Tier III**
Tier I *plus* Tier II *plus*
home visits conducted by non medical staff and/or volunteers*

**Tier IV**
Tier III *plus*
community health nurses supervising Tier III staff & supporting patients at home

*This is developed by the site with specific guidelines from AIDSRelief*
Year 1 - initial start up

- Tier I (n=8): 14%
- Tier II (n=3): 10%
- Tier III (n=9): 5%
- Tier IV (n=7): 1%

Percent lost to follow up (n=27 sites)

Year 5 - follow up

- Tier I (n=0): 4.2%
- Tier II (n=20): 4.1%
- Tier III (n=31): 2.2%
- Tier IV (n=92): 0%

Percent lost to follow up (n=143 sites)

Sites with fewer support systems had greater loss to follow up.
Durability of Initial Regimen: Key Factors

• Regimen Choice
• Care Delivery System
  – Role of enhanced treatment preparation and treatment support especially during induction of viral control
• Treatment Strategy
What we learned about: Treatment Strategy

- Baseline CD4 and viral suppression rates
- Higher the initial CD4, greater the chances of increasing durability

Viral Suppression Rates

<table>
<thead>
<tr>
<th>CD4 Range</th>
<th>Suppression Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>85.9</td>
</tr>
<tr>
<td>51-100</td>
<td>84.9</td>
</tr>
<tr>
<td>101-200</td>
<td>89.2</td>
</tr>
<tr>
<td>201-350</td>
<td>89.4</td>
</tr>
<tr>
<td>&gt;351</td>
<td>90.6</td>
</tr>
</tbody>
</table>

N=7,513
Talk Outline

- Background ARV
- Importance of HIV viral suppression
- Second Line Treatment
- Future treatment Strategies
Growing challenges for successful second line treatment

Need to optimize durability of first line regimen
- Regimen choice
- Treatment strategy
- Care Delivery system

Key Challenges
- Initial wide scale use of cell cycle dependent ARVs
- Use of clinical failure to define treatment failure
- Dead end mutations versus mutation evolution

It is very simple to make HIV care and treatment complicated.
It is a little more complicated, at first, to keep HIV care and treatment simple.
Approach to Second Line Treatment

- China’s second line regimens: TDF/3TC/Kaletra or AZT/3TC/Kaletra

- Approach to Second Line ARV Treatment
  - Regimen prior to failure key
  - ARV failure or adherence failure
  - Regimen Choice
    - Role of protease inhibitors
    - Role of integrase inhibitors
      - Raltegravir
      - Elvitegravir/cobicistat
      - Dolutegravir
    - Role of maintaining decrease replication capacity mutations
    - 184V and K65R
Implications of Stages of Treatment Failure with AZT/ D4T, 3TC and Nev/Efv

Remaining Treatment Options

AZT/d4T, 3TC, NEV/EFV

Early Virologic Failure

NRTIs: ABC, AZT, ddI, d4T, TDF
NNRTIs: None
PIs: All
INT: All

Clinical Failure (Late Virologic Failure)

NRTIs: None
NNRTIs: None
PIs: All
INT: All
Implications of Stages of Treatment Failure with TDF, 3TC and Nev/Efv

Remaining Treatment Options

NRTIs: ABC, AZT, ddI, d4T, TDF
NNRTIs: None
PIs: All
INT: All

Early Virologic Failure

NRTIs: AZT
NNRTIs: None
PIs: All
INT: All

Clinical Failure
(Late Virologic Failure)

TDF, 3TC, /NevEFV
Resistance Patterns after Initial Failure of Common NRTI Backbones
Role of Dead End Mutations

AZT/3TC
D4T/3TC

M184V → Multiple TAMS

TDF/FTC

M184V → K65R

ABC/3TC

M184V → 74V > K65R

TIME TO DEVELOPMENT
Talk Outline

• Background ARV
• Importance of HIV viral suppression
• Second Line Treatment
• Future treatment Strategies
Identification of Host Proteins Required for HIV Infection through a Functional Genomic Screen

234 new and 38 known host targets identified that are necessary for HIV replication

Resveratrol enhances Tenofovir susceptibility

<table>
<thead>
<tr>
<th></th>
<th>RV 0</th>
<th>RV 10 µM</th>
<th>RV 20 µM</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF IC&lt;sub&gt;50&lt;/sub&gt; (µM)</td>
<td>0.35</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>TDF IC&lt;sub&gt;90&lt;/sub&gt; (µM)</td>
<td>2</td>
<td>0.5</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Resveratrol restores Tenofovir susceptibility of multi-drug resistant viruses

<table>
<thead>
<tr>
<th></th>
<th>RV 0</th>
<th>RV 10 μM</th>
<th>RV 20 μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF IC_{50} (μM)</td>
<td>3</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>TDF IC_{90} (μM)</td>
<td>20</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>
Humanized Mouse Model

HIV-1 (41L, 44D, 67N, 69D, 210W, 215Y)

HIV RNA (copies/ml)

Day 15

VEHICLE

TDF (100 mg/kg)

TDF (100 mg/kg) + TARV (25 mg/kg)

(50 copies/ml)
Evolution of the Therapeutic Goal Line

- **In vivo Antiviral activity** (1985-1995)
- **Dosing and regimen simplification** (2003-2005)
- **Long term durability** (2005-present)
  - Durable viral suppression
  - Limited chronic toxicity profile
  - Expanded use of morbidity friendly agents
- **Broadening indications** (2010-2015)
  - Expanded treatment recommendations- treat all HIV infected pts.
  - Treatment as Prevention to include PrEP
- **Future** (2015-2020)
  - Expanded therapeutic targets – targeting host cell pathways
  - Development of Therapeutic Strategies to decrease pro-viral copy number and reservoir of infection towards “functional cure”
"I think you should be more explicit here in step two."
Key Take Home Messages: The Shift Toward Earlier Initiation of Antiretroviral Therapy

• Newer ART regimens
  – Better tolerated, more convenient, and more potent than older regimens

• Durability and Survival benefit
  – Randomized controlled trials and observational cohort data

• Prevent reactivation of TB, and TB related morbidity and mortality
  – Key opportunity to impact TB epidemic

• Biologic rationale and negative impact of chronic replication and chronic inflammation
  – Untreated HIV has increased risk of HIV related KS, non-Hodgkin's lymphoma, and possibility of non-AIDS cancers and accelerated CVD, liver/kidney disease and aging

• Effective ART reduces HIV transmission
  – Key component of overall strategy to end epidemic

• Evidence that early treatment impacts HIV reservoir and potential for future functional cure
Thank you