APACC 2016
HIV drug resistance

Shinichi Oka, MD, PhD.
AIDS Clinical Center (ACC)
National Center for Global Health and Medicine (NCGM)
1. Current situation of ART and TDR in Japan
2. Current situation of ART and TDR in Vietnam
3. Basic understandings of acquired DRMs
4. How to stop EFV without inducing DRM
Changes of NRTIs for initial therapy in the past two decades

- d4T+3TC
- ABC+3TC
- TDF+XTC
Recent trends of NRTIs usage in May
Changes of key drugs for initial therapy in the past two decades

NNRTI

PI

INSTI

- EFV
- LPV
- DRV
- DTG
Recent trends of key drugs usage in May

The chart shows the use ratio (%) of various drugs over the years from 2008 to 2015. The drugs are represented by different colors:
- others
- DTG(TRI)
- EVG(STB)
- RAL
- DRV
- FPV
- ATV
- RPV(CMP)
- ETR
- LPV/r
- EFV

The percentages are indicated along the y-axis, ranging from 0% to 100%.
CD4 counts in patients on cART in ACC

>200/μL: 94.7%

>500/μL: 52.2%
HIV-RNA in patients on cART in ACC

Most patients are well controlled with current cART

- undetectable: 84.7%
- <200 c/mL: 96.8%

*just started cART in 10 cases
90-90-90 and Cascade of care at ACC

Problem in Japan

Acquired drug resistance is NOT a major issue of ART in Japan

ACC data
Characteristics of Transmitted Drug-Resistant HIV-1 in Recently Infected Treatment-Naive Patients in Japan

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Rumi Minami, MD, PhD,¶ Kazue Uchida, PhD,# Kenji Sadasasu, PhD,** Makiko Kondo, PhD,††
and Wataru Sugiura, MD, PhD,*†‡§§ the Japanese Drug Resistance HIV-1 Surveillance Network

(J Acquir Immune Defic Syndr 2016;71:367–373)

Trends in transmitted drug-resistant HIV-1 and demographic characteristics of newly diagnosed patients: Nationwide surveillance from 2003 to 2008 in Japan

Junko Hattori a, Teiichiro Shiino b, Hiroyuki Gatanaga c, Shigeru Yoshida d, Dai Watanabe e,
Rumi Minami f, Kenji Sadasasu g, Makiko Kondo h, Haruyo Mori i, Mikio Ueda j, Masao Tateyama k,
Atsuhisa Ueda l, Shingo Kato m, Toshihiro Ito n, Masayasu Oie o, Noboru Takata p, Tsunefusa Hayashida c,
Mami Nagashima g, Masakazu Matsuda q, Shiro Ibe a, Yasuo Ota r, Satoru Sasaki n,
Yoshiaki Ishigatsubo l, Yoshinari Tanabe o, Ichiro Koga r, Yoko Kojima l, Masahiro Yamamoto f,
Jiro Fujita k, Yoshiyuki Yokomaku a, Takao Koike s, Takuma Shirasaka e, Shinichi Oka c, Wataru Sugiura a,b,t,*

Antiviral Research 88 (2010) 72–79
Annual prevalence of TDR HIV in Japan between 2003 and 2012
NRTI resistant mutations in newly diagnosed cases

<table>
<thead>
<tr>
<th>NRTI</th>
<th>n</th>
<th>(%)</th>
</tr>
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<tbody>
<tr>
<td>M41L</td>
<td>11</td>
<td>(0.4)</td>
</tr>
<tr>
<td>K65R</td>
<td>1</td>
<td>(0.0)</td>
</tr>
<tr>
<td>D67N/G/E</td>
<td>7</td>
<td>(0.3)</td>
</tr>
<tr>
<td>T69D</td>
<td>8</td>
<td>(0.3)</td>
</tr>
<tr>
<td>69INS</td>
<td>1</td>
<td>(0.0)</td>
</tr>
<tr>
<td>K70R/E</td>
<td>2</td>
<td>(0.1)</td>
</tr>
<tr>
<td>L74V/I</td>
<td>3</td>
<td>(0.1)</td>
</tr>
<tr>
<td>V75A/M</td>
<td>2</td>
<td>(0.1)</td>
</tr>
<tr>
<td>Y115F</td>
<td>3</td>
<td>(0.1)</td>
</tr>
<tr>
<td>M184V/I</td>
<td>12</td>
<td>(0.5)</td>
</tr>
<tr>
<td>L210W</td>
<td>5</td>
<td>(0.2)</td>
</tr>
<tr>
<td>T215X</td>
<td>81</td>
<td>(3.2)</td>
</tr>
<tr>
<td>K219Q/E/N/R</td>
<td>4</td>
<td>(0.2)</td>
</tr>
</tbody>
</table>
NNRTI and PI resistant mutations in newly diagnosed cases

<table>
<thead>
<tr>
<th>NNRTIa</th>
<th>Count</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>L100I</td>
<td>1</td>
<td>(0.0)</td>
</tr>
<tr>
<td>K101E</td>
<td>2</td>
<td>(0.1)</td>
</tr>
<tr>
<td>K103N</td>
<td>14</td>
<td>(0.6)</td>
</tr>
<tr>
<td>V106A/M</td>
<td>1</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Y181C/I/V</td>
<td>3</td>
<td>(0.1)</td>
</tr>
<tr>
<td>P225H</td>
<td>1</td>
<td>(0.0)</td>
</tr>
<tr>
<td>P236L</td>
<td>1</td>
<td>(0.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PIa</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>L24I</td>
<td>1</td>
<td>(0.0)</td>
</tr>
<tr>
<td>D30N</td>
<td>5</td>
<td>(0.2)</td>
</tr>
<tr>
<td>V32I</td>
<td>3</td>
<td>(0.1)</td>
</tr>
<tr>
<td>M46I/L</td>
<td>44</td>
<td>(1.7)</td>
</tr>
<tr>
<td>I47V/A</td>
<td>2</td>
<td>(0.1)</td>
</tr>
<tr>
<td>V82A/L</td>
<td>2</td>
<td>(0.1)</td>
</tr>
<tr>
<td>I85V</td>
<td>5</td>
<td>(0.2)</td>
</tr>
<tr>
<td>N88D/S</td>
<td>7</td>
<td>(0.3)</td>
</tr>
<tr>
<td>L90M</td>
<td>4</td>
<td>(0.2)</td>
</tr>
</tbody>
</table>
Current situation of ART and TDR in Japan

1. A key drug of the first line ART is changing over time.
2. PIs were the most frequently used in this decade.
3. However recently, INSTI has been mainly selected.
4. Current ART have been very effective in terms of viral suppression. Almost all patients on ART achieved VL suppression below 20 copies/ml.
5. Annual prevalence of TDR has been slightly increasing but still below 10% in the past two years.
HIV drug resistance

1. Current situation of ART and TDR in Japan
2. Current situation of ART and TDR in Vietnam
3. Basic understandings of acquired DRM's
4. How to stop EFV without inducing DRM
Expand of cART and new cases in Vietnam

250,000 cases were reported as of DEC 2011
Hanoi cohort in National Hospital of Tropical Diseases - HIV-infected patients on ART were enrolled -

Background:
1. Number of patients on ART is expanding rapidly
2. ART is implemented based on WHO guidelines
3. CRF01-AE is predominant

What to follow;
1. Monitoring of ART
2. Side effects due to ART in Vietnamese
True LTFU: patients who stopped visiting the clinics for at least 3 months after their last visit, and did not return by the end of the follow-up period (December 31, 2013).
Conclusion
ADIs were not rare in spite of being on effective ART. Age over 50 years, but not IDU history, was associated with shorter survival in the cohort. This study provides in-depth data on the prognosis of patients on ART in Vietnam during the first decade of ART scale-up.

RESEARCH ARTICLE

Junko Tanuma1,2*, Kyu Ha Lee3, Sebastien Haneuse4, Shoko Matsumoto1, Dung Thi Nguyen5, Dung Thi Hoai Nguyen5, Cuong Duy Do6, Thuy Thanh Pham6, Kinh Van Nguyen5, Shinichi Oka1

Table 2. Incidence Rates of AIDS-Defining Opportunistic Infections during ART.

<table>
<thead>
<tr>
<th>AIDS-defining illnesses (ADIs)</th>
<th>Number of episodes</th>
<th>Incidence Rate (1/1000 PYS)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n = 1,197; 3,446 person-years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any ADIs</td>
<td>161</td>
<td>48.7</td>
<td>(39.8–54.5)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>98</td>
<td>28.4</td>
<td>(23.1–34.7)</td>
</tr>
<tr>
<td>Toxoplasmosis of brain</td>
<td>16</td>
<td>4.64</td>
<td>(2.65–7.54)</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>10</td>
<td>2.90</td>
<td>(1.39–5.34)</td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>7</td>
<td>2.03</td>
<td>(0.82–4.19)</td>
</tr>
<tr>
<td>Cytomegalovirus retinitis</td>
<td>8</td>
<td>1.74</td>
<td>(0.64–3.79)</td>
</tr>
<tr>
<td>Mycobacterium avium complex</td>
<td>6</td>
<td>1.74</td>
<td>(0.64–3.79)</td>
</tr>
<tr>
<td>Recurrent bacterial pneumonia</td>
<td>5</td>
<td>1.45</td>
<td>(0.47–3.39)</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>4</td>
<td>1.16</td>
<td>(0.32–2.97)</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>2</td>
<td>0.58</td>
<td>(0.070–2.10)</td>
</tr>
<tr>
<td>Progressive multifocal leuкоencephalopathy</td>
<td>2</td>
<td>0.58</td>
<td>(0.070–2.10)</td>
</tr>
<tr>
<td>Disseminated HSV infection</td>
<td>2</td>
<td>0.58</td>
<td>(0.070–2.10)</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>1</td>
<td>0.29</td>
<td>(0.007–1.82)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>1</td>
<td>0.29</td>
<td>(0.007–1.82)</td>
</tr>
<tr>
<td>Salmonella septicaemia</td>
<td>1</td>
<td>0.29</td>
<td>(0.007–1.82)</td>
</tr>
</tbody>
</table>

Fig 1. Survival Probabilities on ART in All Study Participants. (a) Survival without new AIDS events on ART. (b) Overall survival on ART. Dotted lines indicate ranges of 95% CIs.
Consecutive 300 newly diagnosed cases were enrolled each year.

**Conclusions:** There was no increase in TDR prevalence in Southern Vietnam during and after the 2008–2012 rapid scale up of ART.
Current situation of ART and TDR in Vietnam

1. ART is expanding rapidly in this decade. Annual new cases have been decreasing since 2007.
2. Patient cohorts revealed very high retention rate and low true LTFU (3.1%)
3. First line ART was very effective. However, there were still ADIs including TB.
4. Prevalence of TDR during 2008-2012 was still low (4.2%).
HIV drug resistance

1. Current situation of ART and TDR in Japan

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3. Basic understandings of acquired DRM

4. How to stop EFV without inducing DRM
Treatment success with NFV+AZT+3TC (ITT)

- NFV: 10 tablets/day
- AZT: 4 capsules/day
- 3TC: 2 tablets/day
- Total: 16 tablets/day

Emergence of primary mutation of NFV

Proportion of patients without primary mutations

Time after commencement of therapy (weeks)

No. at risk

D30N only 51 47 44 42 41 41 41 41 41 41 41 10
L90M only 51 51 51 51 50 50 49 47 47 46 46 5
D30N and/or L90M 51 47 44 42 41 41 40 39 39 39 39 12

VL at week 12 and emergence of drug resistance

A: viral load < 400 copies/ml at week 12

B: viral load > 400 copies/ml at week 12

Proportion of patients without primary mutations

Time after commencement of therapy (weeks)

No. at risk

A

B*

No. of cases with censored data

No. of cases with mutation

Time lag of DRMs emergence in plasma and PBMC, and VL

Time lag of DRMs emergence in plasma and PBMC

Viral load (/ml)

Bi, Oka et al. JAIDS 34: 1-6, 2003
Prevalence of DRMs in naïve and primary Pts

### DRMs in pre-treatment patients (PDR)

<table>
<thead>
<tr>
<th>Region</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT region</td>
<td>6/237</td>
<td>2.5%</td>
</tr>
<tr>
<td>PR region</td>
<td>5/248</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

### DRMs in primary infected patients (TDR)

<table>
<thead>
<tr>
<th>Region</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT region</td>
<td>2/24</td>
<td>8.3%</td>
</tr>
<tr>
<td>PR region</td>
<td>2/24</td>
<td>8.3%</td>
</tr>
<tr>
<td>RT or/and PR regions</td>
<td>3/24</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

Ida, Oka et al. (unpublished data)
Time to disappearance of DRMs after cessation of ART

Basic understandings of acquired DRMs

1. Adherence is the most important factor for ARD. Pill burden, side effects, etc.
2. VL at week 12 after initiation of ART is critical for treatment success
3. ADRMs appear in plasma first and then in PBMC under drug selection pressure
4. ADRMs disappear in plasma first and then in PBMC under no drug selection pressure
HIV drug resistance

1. Current situation of ART and TDR in Japan
2. Current situation of ART and TDR in Vietnam
3. Basic understandings of acquired DRM
4. How to stop EFV without inducing DRM
How to stop ART

Of course, ART should not be interrupted. However, at the extremely situations such as natural disaster or budget depletion, and if drug supply was stopped ----,

When discontinue ART, in general, stop all drugs simultaneously in order to avoid inducing drug-resistance.
How to stop ART

Of course, ART should not be interrupted. However, at the extremely situations such as natural disaster or budget depletion, and if drug supply was stopped ----,

When discontinue ART, in general, stop all drugs simultaneously in order to avoid inducing drug-resistance except EFV.
Efavirenz (EFV)

Advantages

Single Tablet Regimen (EFV/TDF/FTC)
Reasonable price

Disadvantages

CNS side effects
Easy development of resistance

Only a single mutation is required to confer high-level NNRTI resistance.
EFV-ART with Poor Adherence

Viral Load (copies/ml)

EFV+TDF/FTC

K103N
EFV Resistance after Interrupting Therapy

Viral Load (copies/ml)

EFV+AZT+ddI

CD4 (/mm³)

K103N

liver damage

0 100 200 300 400

Sep 2001 2002 2003

Sep 2003

Mar

10^2

10^3

10^4

10^5

10^6

10^4

10^3

10^2
Emergence of K103N after cessation of EFV

Do not stop all drugs simultaneously, when stop EFV-containing regimen.

Viruses replicating under EFV selective pressure.
How to avoid inducing EFV resistance

When discontinue EFV-based HAART,

1. Stop EFV first before the other drugs

2. Substitute EFV with PI prior to interruption
Stopping EFV first before the other agents

Ideally, almost simultaneously disappear.

Viruses replicating under no selection pressure.

Viral Load (copies/ml)

10^6

10^5

10^4

10^3

10^2

10^1

10^0

EFV+AZT+ddI

AZT+ddI

about 1 weeks

EFV+AZT+ddI

AZT+ddI
Substitute EFV with PI prior to interruption

Viral Load (copies/ml)

- EFV
- AZT+ddI
- DRV+rtv

Viruses begin to replicate under no selection pressure.

- EFV+AZT+ddI
- DRV+rtv+AZT+ddI

about 1 weeks
Homozygous CYP2B6 *6 (Q172H and K262R) correlates with high plasma efavirenz concentrations in HIV-1 patients treated with standard efavirenz-containing regimens

Kiyoto Tsuchiya, Hiroyuki Gatanaga, Natsuo Tachikawa, Katsuji Teruya, Yoshimi Kikuchi, Munehiro Yoshino, Takeshi Kuwahara, Takuma Shirasaka, Satoshi Kimura, and Shinichi Oka

BBRC 319: 1322-1326, 2004
Interruption of EFV in CYP2B6 516TT holders

- Viruses replicating under EFV selective pressure.
- Higher conc.
- EFV
- Viral Load (copies/ml)
- AZT+ddI
- Extremely longer functional monotherapy
- K103N
How to stop EFV without inducing DRM

1. EFV is the most widely used ARV in the world.
2. Basically, EFV should not be interrupted.
3. If we have to stop EFV,
   - Substitute EFV with PI prior to interruption
   - Stop EFV first around 1 week before the other drugs
   - pay special attention to slow EFV metabolizers
HIV drug resistance

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