Adverse Effects and Treatment Strategies During Long Term ART

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Beijing DiTan Hospital, Capital Medical University
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Outline

01. Grand goals and limited ARVs

02. Adverse effects: a common problem faced by physicians and patients

03. Integrase inhibitors: a new era of HARRT

04. Common adverse effects of ARVs and treatment strategies
Goals of Antiretroviral Therapy

1. Maintain or restore the health of people living with HIV-1 (PLWHIV) through suppression of HIV-1 replication

2. Minimize or eliminate short and long-term adverse effects of the therapy

3. Have therapies that are accessible to all PLWHIV

4. Prevent transmission of HIV-1 to others via any route of exposure
Nearly 20 ARVs of four categories have come into the domestic market at present

<table>
<thead>
<tr>
<th>Drug categories</th>
<th>Commonly used drugs</th>
<th>Marketing status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>Zidovudine, lamivudine, abacavir, tenofovir, emtricitabine, etc.</td>
<td></td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Efavirenz, etravirine, rilpivirine</td>
<td>marketed</td>
</tr>
<tr>
<td>PIs</td>
<td>Ritonavir, tipranavir, atazanavir, etc.</td>
<td></td>
</tr>
<tr>
<td>INTIs</td>
<td>Raltegravir, dolutegravir</td>
<td></td>
</tr>
<tr>
<td>FIs</td>
<td></td>
<td>not yet marketed</td>
</tr>
<tr>
<td>CCR5 inhibitors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NRTI: nucleoside reverse-transcriptase inhibitor; NNRTI: non-nucleoside reverse-transcriptase inhibitor; PI: protease inhibitor; FI: fusion Inhibitor; INTI: integrase inhibitor; CCR5: chemokine receptor 5

Limited treatment options

<table>
<thead>
<tr>
<th>NRTI DUAL BACKBONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/ AZT (generic) + 3TC (generic)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3rd Agent– NNRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line</td>
</tr>
<tr>
<td>EFV (generic)</td>
</tr>
<tr>
<td>NVP (generic)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3rd Agent– PIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd line</td>
</tr>
<tr>
<td>LPV/r</td>
</tr>
</tbody>
</table>

NRTI: nucleoside reverse-transcriptase inhibitor; TDF: tenofovir disoproxil fumarate; 3TC: lamivudine; NNRTI: non-nucleoside reverse-transcriptase inhibitor; PI: protease inhibitor; EFV: efavirenz; NVP: nevirapine; LPV/r: lopinavir/ritonavir.
Most of ARVs have prominent side effects leading to decline in the quality of life and treatment adherence of patients with HIV

ARVs related adverse effects are widely distributed\textsuperscript{1-4}

- Adverse effects such as diarrhoea, anaemia, lipodystrophy syndrome, etc. are associated with decreased quality of life among patients\textsuperscript{2,5}
- Central nervous system adverse effect is one factor that affects patients' quality of life\textsuperscript{6}
- Side effect is an independent risk factor associated with non-adherence to ART\textsuperscript{7}

ART: antiretroviral therapy; NRTIs: nucleoside reverse-transcriptase inhibitors; NNRTIs: non-nucleoside reverse-transcriptase inhibitors; PIs: protease inhibitors; INIs: integrase inhibitors.

Challenges with treatment outcome

• Discontinuation of EFV as first line treatment
  • Prescribing information
    1.7% discontinued due to rash
    2.1% discontinued EFV due to nervous system symptoms
    1% discontinued EFV due to psychiatric disorders
  • Study information
    20% discontinue EFV in a study conducted in 2012
    CNS toxicity is the major reason
• Switch to 2nd line treatment too early

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1. Atripla® Prescribing Information. Bristol-Myers Squibb and Gilead, 2010
3. Patients number distribution, sources from NCAIDS
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China: nonadherence to ART is mainly due to drug’s side effects

To understand the interrelated factors that influence the treatment compliance of patients with HIV infection in China, this study investigated drug adherence, side effect and clinical manifestation of the patients who have or not have received ART for 2-12 months in AIDS high incidence areas.

Meta-analysis: adverse drug events had a serious impact on treatment adherence

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Pooled OR (95% CI)</th>
<th>P value (OR)</th>
<th>F (%)</th>
<th>No. of included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>0.65 (0.53, 0.79)</td>
<td>&lt;0.001</td>
<td>0.00</td>
<td>2</td>
</tr>
<tr>
<td>Dermatological</td>
<td>0.96 (0.61, 1.52)</td>
<td>0.876</td>
<td>62.40</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.63 (0.43, 0.92)</td>
<td>0.016</td>
<td>52.80</td>
<td>3</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>0.74 (0.43, 1.26)</td>
<td>0.270</td>
<td>72.80</td>
<td>2</td>
</tr>
<tr>
<td>Non-specific</td>
<td>0.62 (0.46, 0.83)</td>
<td>0.001</td>
<td>72.80</td>
<td>12</td>
</tr>
<tr>
<td>Sexual dysfunction*</td>
<td>0.72 (0.51, 1.03)</td>
<td>0.037</td>
<td>72.80</td>
<td>2</td>
</tr>
</tbody>
</table>

The effects of general AEs on adherence
OR = 0.72

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Pooled OR (95% CI)</th>
<th>P value (OR)</th>
<th>F (%)</th>
<th>No. of included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbness*</td>
<td>0.92 (0.64, 1.32)</td>
<td>0.665</td>
<td>70.20</td>
<td>2</td>
</tr>
<tr>
<td>Pain when swallowing*</td>
<td>0.50 (0.16, 1.56)</td>
<td>0.231</td>
<td>44.90</td>
<td>1</td>
</tr>
<tr>
<td>Taste disturbances*</td>
<td>0.49 (0.30, 0.77)</td>
<td>0.003</td>
<td>21.90</td>
<td>2</td>
</tr>
<tr>
<td>Tingling in mouth and tongue*</td>
<td>0.67 (0.42, 1.05)</td>
<td>0.079</td>
<td>25.30</td>
<td>1</td>
</tr>
</tbody>
</table>

The effects of sensory AEs on adherence
OR = 0.67

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Pooled OR (95% CI)</th>
<th>P value (OR)</th>
<th>F (%)</th>
<th>No. of included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>0.63 (0.41, 0.95)</td>
<td>0.028</td>
<td>66.90</td>
<td>3</td>
</tr>
<tr>
<td>Confusion</td>
<td>0.35 (0.18, 0.66)</td>
<td>0.001</td>
<td>25.90</td>
<td>2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.65 (0.35, 1.22)</td>
<td>0.177</td>
<td>71.90</td>
<td>2</td>
</tr>
</tbody>
</table>

The effects of mental health AEs on adherence
OR = 0.65

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Pooled OR (95% CI)</th>
<th>P value (OR)</th>
<th>F (%)</th>
<th>No. of included studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain*</td>
<td>0.49 (0.16, 1.57)</td>
<td>0.231</td>
<td>47.70</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhoea*</td>
<td>0.94 (0.79, 1.11)</td>
<td>0.448</td>
<td>0.00</td>
<td>2</td>
</tr>
<tr>
<td>Loss of appetite*</td>
<td>0.54 (0.32, 0.93)</td>
<td>0.027</td>
<td>60.60</td>
<td>3</td>
</tr>
<tr>
<td>Nausea*</td>
<td>0.57 (0.43, 0.77)</td>
<td>&lt;0.001</td>
<td>36.60</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting*</td>
<td>0.97 (0.49, 1.92)</td>
<td>0.305</td>
<td>18.50</td>
<td>1</td>
</tr>
</tbody>
</table>

The effects of gastrointestinal AEs on adherence
OR = 0.49

AEs: adverse events.
Adverse drug reactions significantly decreased quality of life in patients with HIV/AIDS


It indicated that adverse drug reaction is becoming an important factor influencing patients’ QOL.

This study aims to explore the medication status of AIDS patients and the factors influencing their quality of life (QOL). From March to August 2013, in some designated AIDS medical institutions of Harbin, by random sampling method, a self-made questionnaire and WHO QOL- HIV- BREF were used to investigate the medication status of patients taking antiviral drugs, their QOL and its influencing factors.
Cost of treating adverse event is a great economic burden for HIV patients

This study recruited 100 patients with HIV/AIDS receiving HAART in Shanxi. Safety and efficacy monitoring was conducted at the end of weeks 1, 2, 4, 8, 12, 24, 36, 48 and 52 during a one-year follow-up period. Related adverse reactions in patients were treated by the physicians and the data on direct costs of HAART were collected.

AE: adverse event; ARV: antiretroviral (drug).

### Composition of total cost for treatment of patients

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost (Yuan)</th>
<th>Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretroviral drugs</td>
<td>17 780.0</td>
<td>67.0</td>
</tr>
<tr>
<td>Efficacy monitoring</td>
<td>7 000.0</td>
<td>26.4</td>
</tr>
<tr>
<td>Safety monitoring</td>
<td>939.5</td>
<td>3.5</td>
</tr>
<tr>
<td>AE treatment</td>
<td>801.8</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26 521.3</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

### Cost composition for AE treatment of 100 subjects

<table>
<thead>
<tr>
<th>Category</th>
<th>Cost (Yuan)</th>
<th>Comp. (%)</th>
<th>Avg. (Yuan per person)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Property of AE: ARVs related opportunistic infection (prevention &amp; cure)</td>
<td>48 123.8</td>
<td>60.0</td>
<td>481.2</td>
</tr>
<tr>
<td>others</td>
<td>22 950.9</td>
<td>28.6</td>
<td>229.5</td>
</tr>
<tr>
<td><strong>subtotal</strong></td>
<td><strong>80 178.4</strong></td>
<td><strong>100.0</strong></td>
<td><strong>801.7</strong></td>
</tr>
<tr>
<td>AE cost: drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nursing</td>
<td>41 785.4</td>
<td>52.1</td>
<td>417.8</td>
</tr>
<tr>
<td>hospitalization</td>
<td>9 172.0</td>
<td>11.4</td>
<td>91.7</td>
</tr>
<tr>
<td>laboratory test</td>
<td>8 842.0</td>
<td>11.0</td>
<td>88.4</td>
</tr>
<tr>
<td>diagnosis and treatment examination</td>
<td>7 910.0</td>
<td>9.9</td>
<td>79.1</td>
</tr>
<tr>
<td>medical supplies</td>
<td>4 391.7</td>
<td>5.5</td>
<td>43.9</td>
</tr>
<tr>
<td>transfusion</td>
<td>4 159.0</td>
<td>5.2</td>
<td>41.6</td>
</tr>
<tr>
<td><strong>subtotal</strong></td>
<td><strong>80 178.4</strong></td>
<td><strong>100.0</strong></td>
<td><strong>801.7</strong></td>
</tr>
</tbody>
</table>

In rural areas, cost of treating AE is about **30%** of each farmer’s net income per year.
Subjects: adult patients with HIV infection in homosexual who started ART using AZT/TDF+3TC+EFV as initial therapy from 2012.

Drug switch (except switch due to pregnancy):
- AZT+3TC+EFV: 23.5%
- Other: 10.5%

Adverse events occurred:
- AZT+3TC+EFV: 30.5%
- Other: 23.3%

Switch because of AEs (except switch due to pregnancy):
- AZT+3TC+EFV: 16.5%
- Other: 6.2%

The incidence rates of adverse events and drug switches during 2-year treatment (%)

Fujie Zhang unpublished.
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04. Common adverse effects of ARVs and treatment strategies
Integrase inhibitors have gained a leading role in HIV antiretroviral therapy (ART) because of favourable clinic characteristics: high antiviral potency with rapid HIV RNA declines, good tolerability, a favourable safety profile and absence of significant drug-drug interactions as well as targeting a new mode of action hence lacking cross-resistance to other drug classes.

Considerations of new drugs for HIV treatment at present

- Improved tolerability facilitates adherence
- Improved safety reduces long-term toxicity
- Fewer drug interactions improve the efficiency of concomitant medications
- Improved efficacy reduces the risk of failure and drug resistance

Integrase inhibitors: a brand new therapeutic target, high selectivity, low toxicity, decreased cross resistance\textsuperscript{1, 2}

1. Integrase inhibitors exhibit high selectivity since they are only present in the virus with lack of similar enzymes in mammals.

   Ensuring treatment efficacy and lower toxicity concurrently

2. Different from NRTI, NNRTI and PI, HIV integrase inhibitor aims at a brand new therapeutic target.

   Not easy to produce cross resistance, with a high barrier to drug resistance

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### Cause of non-accidental death for HIV patients

**The epidemic reports of HIV/AIDS deaths 2013 (n = 15271)**

<table>
<thead>
<tr>
<th>Categories</th>
<th>Causes of death</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIDS related infections</strong> (N = 4250, 27.8%)</td>
<td>Other AIDS related diseases and syndromes</td>
<td>1038</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>Pneumocystis pneumonia (PCP)</td>
<td>893</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>Recurrent bacterial pneumonia</td>
<td>677</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>Acute HIV infection syndrome</td>
<td>509</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>Candidiasis</td>
<td>269</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>HIV encephalopathy</td>
<td>255</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Cryptococcosis</td>
<td>171</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Herpes simplex virus infection</td>
<td>96</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Chronic cryptosporidiosis (intestinal tract with diarrhea for &gt;1 months)</td>
<td>67</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Diffuse or extrapulmonary infection, toxoplasmosis encephalopathy</td>
<td>58, 54</td>
<td>0.4, 0.4</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus infection, visceral herpes simplex virus infection</td>
<td>35, 30</td>
<td>0.2, 0.2</td>
</tr>
<tr>
<td></td>
<td>Others (disseminated non tuberculous mycobacteria, chronic cryptosporidiosis,</td>
<td>98</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>progressive multifocal leukoencephalopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory diseases</strong></td>
<td></td>
<td>2987</td>
<td>19.5</td>
</tr>
<tr>
<td><strong>Cardiovascular diseases</strong></td>
<td></td>
<td>2028</td>
<td>13.3</td>
</tr>
<tr>
<td><strong>Malignant tumors</strong></td>
<td></td>
<td>1916</td>
<td>12.5</td>
</tr>
<tr>
<td><strong>Tuberculosis, hepatitides</strong></td>
<td></td>
<td>907, 420</td>
<td>5.9, 2.7</td>
</tr>
<tr>
<td><strong>Others</strong> (n = 1710, 11.2%)</td>
<td>HIV wasting syndrome</td>
<td>507</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>Other digestive system diseases</td>
<td>860</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>Endocrine and metabolic diseases</td>
<td>282</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Histoplasmosis / interstitial pneumonia, drug side effects</td>
<td>28, 21</td>
<td>0.2, 0.1</td>
</tr>
<tr>
<td></td>
<td>Other non-AIDS related deaths</td>
<td>1095</td>
<td>7.2</td>
</tr>
</tbody>
</table>
The number of accidental deaths (10.6%) increased year by year

- Other non disease external causes of deaths (injury, etc.), N = 1286 (1.1%)
- Drug overdose, N = 8657 (7.2%)
- Suicides, N = 2178 (2.3%)
- Non-accidental deaths, N = 107081 (89.4%)
Increased risk of suicide in patients receiving EFV-containing regimens

- EFV treatment was associated with increased risk of suicide
  ✓ low absolute risk

- The incidence of attempted/completed suicide was associated with EFV (HR: 2.58; 95% CI: 0.94 to 7.06; \( P = .06 \))
- Treatment with EFV was also associated with increased risk of death due to injury, drug dependence, or unknown causes

**Multivariate Analysis of Factors Associated With Suicidality in ACTG Clinical Trials**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>( P )值</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomly assigned EFV</td>
<td>2.15 (1.20-3.87)</td>
<td>.01</td>
</tr>
<tr>
<td>Age category, yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>2.82 (1.25-6.34)</td>
<td>.04</td>
</tr>
<tr>
<td>30-44</td>
<td>1.69 (0.81-3.55)</td>
<td></td>
</tr>
<tr>
<td>( \geq 45 )</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>Hx IDU</td>
<td>2.18 (1.11-4.30)</td>
<td>.02</td>
</tr>
<tr>
<td>Psychiatric hx or psychoactive rx</td>
<td>3.90 (2.23-6.82)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

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EFV, efavirenz; Hx, history; IDU, injection drug use; PY, person-years; rx, medication.
Co-infections

Retrospective observational cohort study in China recruited patients in 2010-2011

- HIV infection: 69.8%
- HCV-HIV co-infection: 18.2%
- HBV-HIV co-infection: 8.7%
- Triple infection: 3.3%
1. Digestive system adverse reactions and treatment strategies

2. Bone marrow suppression and treatment strategies
3. Skin toxicity and treatment strategies
4. Nervous system adverse reactions and treatment strategies
5. Liver function damage and treatment strategies
6. Renal injury and treatment strategies
7. Lipid metabolic disorders and treatment strategies
8. Cardiovascular system adverse reactions and treatment strategies
9. Abnormal bone metabolism and treatment strategies
An immediate switch to alternative medicine is required for serious adverse reactions in the digestive system

- AZT and PIs are the most common adverse reactions of gastrointestinal tract

**Treatment strategies**

- Co-administration with food can decrease some adverse reactions of digestive system (EFV should be taken on an empty stomach)
- Symptomatic treatment should be provided for patients with serious side effects
- When metoclopramide, loperamide or other symptomatic treatments have no effect on severe gastrointestinal symptoms such as nausea, vomiting and diarrhea, switch to other medicines

*AZT: zidovudine; PI: protease inhibitor*

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2. Bone marrow suppression and treatment strategies
3. Skin toxicity and treatment strategies
4. Nervous system adverse reactions and treatment strategies
5. Liver function damage and treatment strategies
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2. Bone marrow suppression and treatment strategies
3. Skin toxicity and treatment strategies
4. **Nervous system adverse reactions and treatment strategies**
5. Liver function damage and treatment strategies
6. Renal injury and treatment strategies
7. Lipid metabolic disorders and treatment strategies
8. Cardiovascular system adverse reactions and treatment strategies
9. Abnormal bone metabolism and treatment strategies
EFV and AZT are most commonly associated with neurological, psychiatric symptoms

Selected neuropsychiatric adverse events associated with antiretrovirals

<table>
<thead>
<tr>
<th>Antiretroviral</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common ( &gt; 10% )</strong></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Dizziness, insomnia, vivid dreams, impaired concentration, lightheadedness, headache, aggression, anxiety</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Myopathy</td>
</tr>
<tr>
<td>NRTIs</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Circumoral paraesthesias</td>
</tr>
<tr>
<td><strong>Occasional ( 1- &lt; 10% )</strong></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Memory loss, hallucinations, depression</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Peripheral neuropathy, dysgeusia</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td><strong>Rare ( &lt; 1% )</strong></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Mania</td>
</tr>
<tr>
<td>NRTIs</td>
<td>Mitochondriopathy syndromes</td>
</tr>
</tbody>
</table>

EFV: efavirenz; AZT: zidovudine; NRTI: nucleoside reverse-transcriptase inhibitor; CNS: central nervous system
# Treatment strategies for neuropsychiatric side effects

<table>
<thead>
<tr>
<th>ARV</th>
<th>Treatment strategies</th>
</tr>
</thead>
</table>
| EFV  | • Patients with mental illness should avoid the use of EFV before taking medicine\(^1\)  
• Administration on an empty stomach can reduce the blood concentration: take the medicine 2-3 hours before sleep\(^1\)  
• Avoid mechanical operation 2-4 weeks before taking medicine\(^1\)  
• The stepwise dose increase (W1: 20mg/d, W2: 400mg/d, W3: 600mg/d) could lead to a significant reduction in CNS toxicity\(^2\) |
| AZT  | • Dose reduction or discontinuation\(^2\) |
| RTV\(^2\) | • Boosted PI at lower doses with less common side effects  
• Discontinuation results in complete resolution of the symptoms |
| Kaletra\(^{®2}\) | • Symptoms generally resolved after discontinuation |
| DTG\(^3\) | • Discontinuation |
| RAL\(^2\) | • Generally mild and rarely warrant discontinuation |

- When serious dizziness or insomnia occurs and affects normal life or psychiatric symptoms of patients, switch to alternative medicine\(^4\)
- A switch is needed for patients with limb weakness, sensory loss or reduction of fingertips, or mild hereditary ataxia\(^4\)

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3. GLASGOW 2016: [http://chuansong.me/n/1095679052451](http://chuansong.me/n/1095679052451)
1. Digestive system adverse reactions and treatment strategies
2. Bone marrow suppression and treatment strategies
3. Skin toxicity and treatment strategies
4. Nervous system adverse reactions and treatment strategies
5. **Liver function damage and treatment strategies**
6. Renal injury and treatment strategies
7. Lipid metabolic disorders and treatment strategies
8. Cardiovascular system adverse reactions and treatment strategies
9. Abnormal bone metabolism and treatment strategies
Most of ARVs have the potential to cause liver damage.

Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study. Among 21485 participants receiving ART, 6368 developed chronic liver enzyme elevation.
Switch to other kind of ARV after recovery of liver function

High risk patients
- Monitoring of liver function

Criterion for discontinuation
- Consider discontinuation when transaminase exceeds 5-10 times than normal level

Avoid to use similar liver damaging drugs

Hepatoprotective therapy

After recovery of liver function
- Switch to other drugs

1. Digestive system adverse reactions and treatment strategies
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4. Nervous system adverse reactions and treatment strategies
5. Liver function damage and treatment strategies
6. Renal injury and treatment strategies
7. Lipid metabolic disorders and treatment strategies
8. Cardiovascular system adverse reactions and treatment strategies
9. Abnormal bone metabolism and treatment strategies
Many ARVs may lead to renal injury

<table>
<thead>
<tr>
<th>Renal abnormality</th>
<th>ARV</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Proximal tubulopathy (proteinuria, progressive decline in eGFR, phosphaturia)</td>
<td>TDF</td>
<td>• Progressive decline in eGFR and no other cause</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Confirmed hypophosphoataemia of renal origin and no other cause</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Osteopenia/osteoporosis in the presence of increased urine phosphate leak</td>
</tr>
<tr>
<td>• Nephrolithiasis (crystalluria, haematuria, leucocyturia, loin pain, acute renal insufficiency)</td>
<td>IDV, ATV(DRV)</td>
<td>• Confirmed renal stones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recurrent loin pain +/- haematuria</td>
</tr>
<tr>
<td>• Interstitial nephritis (progressive decline in eGFR, tubular proteinuria/ haematuria, eosinophiluria, leucocyte casts)</td>
<td>IDV, ATV</td>
<td>• Progressive decline in eGFR and no other cause</td>
</tr>
<tr>
<td>• Progressive decline in eGFR</td>
<td>TDF, PI/r</td>
<td></td>
</tr>
</tbody>
</table>

Symptomatic treatment for serious patients
1. Digestive system adverse reactions and treatment strategies
2. Bone marrow suppression and treatment strategies
3. Skin toxicity and treatment strategies
4. Nervous system adverse reactions and treatment strategies
5. Liver function damage and treatment strategies
6. Renal injury and treatment strategies
7. **Lipid metabolic disorders and treatment strategies**
8. Cardiovascular system adverse reactions and treatment strategies
9. Abnormal bone metabolism and treatment strategies
PIs are the major drugs leading to uneven distribution of fat\(^1\)\(^-\)\(^3\)

1. The incidence of fat redistribution was \(8.6\)%\(^1\)

2. Fat atrophy\(^2\)
   - AZT caused a loss of fat
   - EFV can cause fat atrophy

3. Fat deposition\(^2\)
   - Taking PIs and NNRTIs can induce fat deposition

4. Switch to the same class of drugs can't reduce fat deposition

5. Treatment strategy: switch to alternative medicine

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RAL has little effect on blood fats

Synergized action

TDF and NVR could reduce blood fats, but whether they can decrease cardiovascular risk remains to be further studied

TDF: tenofovir; NVR: nevirapine; RAL: raltegravir; DTG: dolutegravir; RPV: rilpivirine; ETV: etravirine; ABC: abacavir; TAF: tenofovir alafenamide; EFV: efavirenz; ATV: atazanavir; RTV: ritonavir; COBI: cobicistat; DRV: darunavir; EVG: Elvitegravir

1. Digestive system adverse reactions and treatment strategies
2. Bone marrow suppression and treatment strategies
3. Skin toxicity and treatment strategies
4. Nervous system adverse reactions and treatment strategies
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6. Renal injury and treatment strategies
7. Lipid metabolic disorders and treatment strategies
8. **Cardiovascular system adverse reactions and treatment strategies**
9. Abnormal bone metabolism and treatment strategies
CVD is the fourth leading cause of death in patients with AIDS.

CVD: cardiovascular disease.
ABC and PIs could induce higher risk of CVD

| 3-6/1000 | • The incidence of MI or CVD after taking ABC and PIs was **3-6/1000** |
| 5.1/1000 | • The incidence of MI in PI group was **5.1/1000** |
| 26%     | • The first 4~6 years of ART were accompanied with an annual increase of **26% MI** |
| 2.06    | • The relative risk of MI in treatment group versus in the untreated group was **2.06** |

ABC: abacavir; PI: protein inhibitor
CVD: cardiovascular disease; MI: myocardial infarction
High risk patients with CVD should select ABC and PIs cautiously

• It should be cautious for high risk patients with CVD to select drugs such as ABC and PIs that have great effects on lipid metabolism.

01

• Regular blood lipid and blood glucose monitoring

02

• Change of lifestyle

03

• Symptomatic treatment

04

ABC: abacavir; PI: protein inhibitor
CVD: cardiovascular disease; MI: myocardial infarction
1. Digestive system adverse reactions and treatment strategies
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TDF and PIs may cause osteoporosis\textsuperscript{1-3}

- TDF and PIs may cause osteoporosis
- Osteoporosis increases the risk of fracture

\textbf{Treatment strategies}

- Patients with high risk of osteoporosis (low birth weight, women, elderly, smoking, drinking, hypogonadism, hyperthyroidism, using hormone) select TDF and PIs with caution\textsuperscript{1}
- Monitoring BMD regularly\textsuperscript{4}
- Nutritional support treatment\textsuperscript{4}

\textsuperscript{4} He MQ, Ke TY. China Medicine and Pharmacy 2016; 6(8):34-37.
Since patients with AIDS need combination therapy for ART, it is difficult to avoid adverse reactions.

Adverse reactions have a great influence on the curative efficacy, prognosis, quality of life and medical expenses of patients.

Treat with adverse effects immediately during ART.

ISENTRESS®, a representative INSTI with proved safety and efficacy, can be used as the preferred HAART drug.
THANK YOU