PV of ARVs
Global Picture

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WHO Training Course for Introducing Pharmacovigilance of HIV Medicines

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Acknowledgements

sources of slide material

Published programme data
WHO Progress report 2009
Francois Venter
Uppsala Monitoring Centre (UMC)
MSF
IeDEA
HIV-NAT
DART study group
WHO HQ – HIV Dept – ATC team
The need for PV of ARVs
# Why we need PV of ARVs

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited therapeutic experience</td>
<td>Large exposure populations</td>
</tr>
<tr>
<td>Accelerated pre-marketing development</td>
<td>Lifelong therapy</td>
</tr>
<tr>
<td>Surrogate marker endpoints</td>
<td>ART Programmes</td>
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<tr>
<td>Combination therapy</td>
<td>- natural cohorts</td>
</tr>
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<td>PV systems to be developed</td>
<td>Existing cohort collaborations</td>
</tr>
</tbody>
</table>
Targets for Antiretroviral Drugs in HIV Life Cycle
## RT Inhibitors - NRTIs

<table>
<thead>
<tr>
<th>Name</th>
<th>Originator Trade Name</th>
<th>Originator Company</th>
<th>Launched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (AZT / ZDV)</td>
<td>Retrovir</td>
<td>Glaxo Smith Kline (GSK)</td>
<td>1987</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>Videx</td>
<td>Bristol-Myers Squibb (BMS)</td>
<td>1991</td>
</tr>
<tr>
<td>Zalcitabine (ddC)</td>
<td>HIVID</td>
<td>Roche</td>
<td>1992</td>
</tr>
<tr>
<td>Stavudive (d4T)</td>
<td>Zerit</td>
<td>BMS</td>
<td>1995</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Epivir</td>
<td>GSK</td>
<td>1998</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>Ziagen</td>
<td>GSK</td>
<td>1999</td>
</tr>
<tr>
<td>Tenofovir DF (TDF)</td>
<td>Viread</td>
<td>Gilead</td>
<td>2000</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>Emtriva</td>
<td>Gilead</td>
<td>2003</td>
</tr>
</tbody>
</table>
## RT Inhibitors - NNRTIs

<table>
<thead>
<tr>
<th>Name</th>
<th>Originator Trade Name</th>
<th>Originator Company</th>
<th>Launched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>Viramune</td>
<td>Boehringer Ingelheim</td>
<td>1996</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Sustiva / Stocrin</td>
<td>BMS</td>
<td>1998</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Rescriptor</td>
<td>Pharmacia, Agouron, Pfizer</td>
<td>1999</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Intelencc</td>
<td>Tibotec</td>
<td>2007</td>
</tr>
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</table>
# Protease Inhibitors

<table>
<thead>
<tr>
<th>Name</th>
<th>Originator Trade Name</th>
<th>Originator Company</th>
<th>Launched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td>Invirase</td>
<td>Hoffmann-La Roche</td>
<td>1995</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Crixivan</td>
<td>Merck</td>
<td>1996</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Norvir</td>
<td>Abbott / GSK</td>
<td>1996</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Viracept</td>
<td>Agouron, Pfizer</td>
<td>1997</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>Agenerase, Prozei</td>
<td>Vertex</td>
<td>1999</td>
</tr>
<tr>
<td>Lopinar + Ritonavir</td>
<td>Kaletra, Aluvia</td>
<td>Abbot</td>
<td>2000</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Reyataz, Zrivada</td>
<td>BMS, Novartis</td>
<td>2003</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Lexiva, Telzir</td>
<td>Vertex</td>
<td>2003</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Aptivus</td>
<td>Boehronegr Ingelheim</td>
<td>2005</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Prezista</td>
<td>Tibotec</td>
<td>2006</td>
</tr>
</tbody>
</table>
Why new drug development in the already existing classes?

- Newer NRTIs have better long-term safety and tolerability than older agents
  - ABC and TDF - less lipoatrophy, lactic acidosis than d4T and ddl

- New NNRTIs have no cross-resistance to existing NNRTIs and they may be better tolerated.
  - Etravirine *versus* Nevirapine and Efavirenz

- New Protease Inhibitors (e.g. Darunavir) have improved resistance profiles, are better tolerated and more convenient
Targets for Antiretroviral Therapy in HIV Life Cycle

Reeves & Piefer, 2005
# New ARV Classes

## Entry Inhibitors

<table>
<thead>
<tr>
<th>Name</th>
<th>Originator Trade Name</th>
<th>Originator Company</th>
<th>Launched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfurvitide</td>
<td>Fuzeon</td>
<td>Trimeris, Roche</td>
<td>2003</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Celsentri, Selzentry</td>
<td>Pfizer</td>
<td>2007</td>
</tr>
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</table>

## Intergrase Inhibitors

<table>
<thead>
<tr>
<th>Name</th>
<th>Originator Trade Name</th>
<th>Originator Company</th>
<th>Launched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir</td>
<td>Isentress</td>
<td>Merck</td>
<td>2007</td>
</tr>
</tbody>
</table>
Drug Regulatory Authorities

Ongoing safety monitoring is a pre-requisite

PH programmes & Clinicians

PV is an extension of patient care
Global collection of ADRs for ARVs
Safety monitoring of ARVs
WHO International Drug Monitoring Programme

• Started in 1968 to prevent drug disasters
  – pooled data from 10 countries with existing spontaneous reporting systems

• 1978 - Scientific & technical operations moved to Sweden
  – Uppsala Monitoring Centre (UMC)
  – Set up as WHO Collaborating Centre for International Drug Monitoring

• Central data repository – Vigibase
  – Holds pharmacovigilance data from 1968 to date
  – Now contains 3.9 million individual case safety reports (ICSRs)
WHO drug monitoring programme
Participating countries 2007
Reporting by regions

Data from 2000 - 2005

Non ICH 16.4%

EU 23.4%
USA 59.9%
Japan 0.2%
### Most reported ARVs

<table>
<thead>
<tr>
<th>INN</th>
<th># reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indinavir</td>
<td>6369</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>5597</td>
</tr>
<tr>
<td>Stavudine</td>
<td>5526</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>4766</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>4561</td>
</tr>
<tr>
<td>Didanosine</td>
<td>4154</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>4094</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>4004</td>
</tr>
<tr>
<td>Abacavir</td>
<td>3052</td>
</tr>
</tbody>
</table>
Regional distribution of ARV reports

Data from a study made by UMC in 2007 covering INNs included in PQP programme, report year 2001-2005

ICH= EU, US, JP + NZ,AUS,CAN
Reported safety events of ARVs differ between ICH & non-ICH countries

? Is this due to:
  – higher under-reporting in non-ICH countries
  – true differences in occurrence of ADRs
  – reporting systems yet to be developed

WE NEED TO FIND OUT!
III

Opportunities
-
ART Cohorts
Advantages of Active AE Surveillance

• Quantification of known adverse events
• Identification of groups at risk
• Documentation of clinical determinants of toxicity

• Generation of comparable data
  – common definitions and terms used in reporting
  – common methodologies

• Potential for development of an open source data base

• Involvement of national regulators in ART scale up

• Provision of additional data to pharmaceutical industry
Possible types of Cohorts

• Programme Cohorts
  – e.g MSF

• Existing Cohort Collaborations
  – e.g IDEA

• Dedicated Research Cohorts
  – e.g HIVNAT; DART

• Nested Cohorts within National ART Programmes
  – e.g Rwanda, Senegal
Countries in which MSF runs HIV/AIDS Projects:

- Guatemala
- Honduras
- Nicaragua
- Peru
- Cambodia
- China
- Indonesia
- Mongolia
- Myanmar/Burma
- Thailand
- Kyrgyzstan
- Bulgaria
- Russia
- Ukraine
- Burkina Faso
- Cameroon
- Democratic Republic of Congo
- Ethiopia
- Kenya
- Malawi
- Mozambique
- Nigeria
- Rwanda
- South Africa
- Uganda
- Zimbabwe
IeDEA - International Epidemiologic Databases to Evaluate AIDS
HIV-NAT
The HIV Netherlands Australia Thailand Research Collaboration

- Nakornping Hospital
- Sanpatong Hospital
- Perinatal HIV Prevention Trial Network (PHPT)

- Chiang Rai Hospital
- Khon Kaen Hospital
- Srinagarind Hospital
- Khon Kaen University

- Chulalongkorn Hospital
- HIVNAT
- Siriraj Hospital
- Bamrasnaradura Institute
- Ramathibodhi Hospital
- Vajira Hospital

- National Pediatric Hospital
- Social Health Clinic
- Phnom Penh, Cambodia
- Queen Sawangwattana Memorial Hospital
DART: Development of AntiRetroviral Therapy in Africa

- MRC/UVRI, Entebbe
  - 1019 patients enrolled
- TASO Entebbe, Entebbe Hospital
- 999 patients enrolled
- UZ Harare, Zimbabwe
  - 999 patients enrolled
- JCRC & IDI Mulago, Kampala
  - 1297 patients enrolled

- MRC CTU & Imperial College London
  - Central coordination
- Rockefeller Foundation
- MRC, UK
- DFID, UK
- GSK, Gilead, BI, Abbot
  - Donation of ARVs
RWANDA National Programme

- ~150,000 adult Rwandans are HIV-positive (3% prevalence)
- National programme established in 2004
- 47,000 persons on ART by December 2007 (68% ART coverage)

- Nested cohort study - within National ART programme
- Nationally representative stratified random sample
- n = 3194 adults (<15 years) initiating ART 1st Jan04 - 31st Dec05

- Median age at ART initiation - 37 years
- 65% female
- Baseline median CD4 count 141 cells /microliter.

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>In active follow up</td>
<td>92%</td>
<td>86%</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>3.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Known to have died</td>
<td>3.6%</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

V

ART Regimen Selection in Programmes
Selection of ARVs in the PH approach

The Concept of Essential Medicines
A limited range of carefully selected essential medicines leads to better healthcare, better drug management, lower costs.

The Public Health Approach to ART
Recommendations on selection of ART regimens:
– When to Start
– When to Substitute
– When to Switch
– When to Stop

Process:
– Evidence-based
– Simplified
– Standardised
Main first-line antiretroviral regimens used among 2.4 million adults in 36 low- and middle-income countries, December 2008

- **d4T + 3TC + NVP**: 45%
- **AZT + 3TC + EFV**: 18%
- **AZT + 3TC + NVP**: 17%
- **d4T + 3TC + EFV**: 11%
- **TDF-based**: 8%
- Others: 1%

*TDF-based regimens: TDF + FTC + NVP (3%), TDF + FTC + EFV (3%), TDF + 3TC + NVP (1%) and TDF + 3TC + EFV (1%).*
Main second-line antiretroviral regimens used among adults (n=51 135) in 36 low- and middle-income countries, December 2008
First-line regimens used among children (n=177,064) in 36 low- and middle-income countries, December 2008

![Bar chart showing frequency of different regimens.]

- d4T + 3TC + NVP: 41%
- AZT + 3TC + NVP: 37%
- AZT + 3TC + FEV: 12%
- d4T + 3TC + EFV: 7%
- ABC + 3TC + LPV/r: 1%
- Others: 2%
Second-line regimens used among children (n=5997) in 35 low- and middle-income countries, December 2008

- ABC + d4T + LPV/r: 28%
- ABC + ddI + LPV/r: 23%
- d4T + 3TC + ddI: 11%
- d4T + 3TC + LPV/r: 8%
- 3TC + ddI + LPV/r: 7%
- AZT + 3TC + LPV/r: 6%
- Others: 17%
IV

Key Gaps in Knowledge

- ART in Resource Limited Settings
Overall

? Rates of ART limiting adverse events

Key challenge:

Laboratory requirements for toxicity monitoring
NRTIs

Zidovudine - rates of anaemia & neutropenia
- efficacy of reduced dosing

Tenofovir DF - safety in pregnancy
- safety in children & adolescents
- rates of renal dysfunction

Stavudine - rates of major known toxicities
- safety and efficacy of reduced dose
NNRTIs

Efavirenz  - safety in pregnancy
           - efficacy & safety of lower dosing

Nevirapine  - safety at higher CD4 counts
            - safety with rifampicin
            - safety & efficacy of o.d dosing
PIs
“new agents”

Protease Inhibitors
  – rates of adverse events
  – optimal dosing & adverse effects with rifabutin

“New” ARV agents [including 3rd line options]
Atazanavir, Darunavir, Raltegravir, Etravirine
  – rates of adverse events in “new” populations