Pharmacovigilance in a Resource-Limited Setting: Approaches to Targeted Spontaneous Reporting for Suspected Adverse Drug Reactions to Antiretroviral Treatment

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Objectives

- Provide a brief description of AMPATH
- Give a background and description of the project
- Review the preliminary results
- Discuss the challenges encountered and lessons learnt
A cademic M odel for P revention A nd T reatment of H IV/A IDS

1/17/2014
Initiated in November 2001
- >250 care sites in western Kenya
  - Catchment population ~ 3.5 million
  - HIV prevalence 0.8 – 30%
  - >140,000 patients ever enrolled with >60,000 on antiretroviral therapy
69% of all the people living with HIV are in Sub-Saharan Africa.

> 8 million HIV-infected patients are now receiving treatment in Low–Middle Income Countries (LMICs).

Little is known about the toxicity profile of these drugs in African populations.

The optimal method for conducting routine pharmacovigilance (PV) in settings with limited healthcare infrastructure is not yet known.

Targeted Spontaneous Reporting (TSR) has been proposed...
Targeted Spontaneous Reporting (TSR)

- Hybrid between spontaneous reporting and cohort event monitoring
- Strategy is focused on specific issues
- Leveraging on existing infrastructures
- Assess the feasibility and challenges encountered during a pilot of various TSR approaches in the collection of SADR data in patients on antiretroviral therapy (ART)
PARTNERS
Study design

Site
- Moi Teaching and Referral Hospital (MTRH)- AMPATH, Eldoret, Kenya

Inclusion criteria
- HIV positive and antiretroviral therapy
- Attend the AMPATH MTRH clinics (4 modules)

Exclusion criteria
- HIV positive but not on antiretroviral therapy
- Attend other AMPATH clinics
Five approaches were piloted:

- TSR 1 - Kenyan Pharmacy and Poisons Board (KPPB) Suspected Adverse Drug Reporting (SADR) form
- TSR 2 - Routine Clinical encounter forms
- TSR 3 - Peer led interviews
- TSR 4 - Pharmaceutical technician led interviews
- TSR 5 - Pharmacy dispensing data
KPPB SADR reporting form (TSR 1)
29q. Side-effects/Toxicity: Any side-effects attributable to any drug that the patient is currently taking? □ Yes □ No
   If Yes, drug(s): ________________________________________________________________

29r. Any side-effects attributable to any drug that the patient has ever taken? □ Yes □ No
   If Yes, drug(s): ________________________________________________________________

29s. If yes, tick all that apply: □ Rash □ Anemia □ Lipo-dystrophy □ Hepatitis □ Neuropathy □ IRIS □ Steven-Johnson syndrome □ Acidosis □ Diarrhea □ Persistent Vomiting □ Other (specify): ________________________________________________________________

29t. Severity of the reaction: □ Mild □ Moderate □ Severe □ Unknown

29u. Cause of the reaction/Toxicity: □ Certain □ Probable/Likely □ Possible □ Unlikely □ Conditional/Unclassified □ Unassessable/Unclassified

30. Physical examination:
Patient Interviews (TSR 3 and 4)

1000 participants

Adults
N= 500

- 1st Line
N= 250
- 2nd Line
N= 50
- Stable
N= 200

Pregnant
N=100

- 1st Line
N= 150
- 2nd Line
N= 50
- Stable
N= 200

Children
N= 400

- 1st Line
N= 200
- 2nd Line
N= 50
- Stable
N= 200
Patient Interviews

- Peers (TSR 3) Vs Pharmaceutical technicians (TSR 4)
- Standardized form are used, including:
  - PV encounter form
  - In-depth symptom screen form
  - Adherence form
  - WHO quality of life form
  - Pregnancy questionnaire
- Data is entered into a database for subsequent analysis and reporting
Patient Interviews

[Image of two individuals in an office setting, one woman and one man, engaged in a conversation. The woman is holding a document and the man is looking at it.]
### In-depth Symptom Screen Form

<table>
<thead>
<tr>
<th>Column 1</th>
<th>Column 2</th>
<th>Column 3</th>
<th>Column 4</th>
<th>Column 5</th>
<th>Column 6</th>
<th>Column 7</th>
<th>Column 8</th>
<th>Column 9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td>Yes or No</td>
<td>Frequency:</td>
<td>Duration:</td>
<td>Medication</td>
<td>Adherence:</td>
<td>Severity of</td>
<td>Action Taken</td>
<td>Outcome</td>
</tr>
<tr>
<td></td>
<td>Are you currently experiencing this problem?</td>
<td>How many times a day, week, or month do you experience or were you experiencing this symptom?</td>
<td>Total time the symptom has occurred to date</td>
<td>associated with this symptom?</td>
<td>Adherence: Have you ever skipped a dose to avoid this symptom?</td>
<td>symptom? (refer to definitions page)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diarrhea</strong> (Increase in number of loose stools)</td>
<td>Yes</td>
<td>Present</td>
<td>Times per Day:</td>
<td>Stop date:</td>
<td>Name of medication:</td>
<td>Yes</td>
<td>Mild</td>
<td>Drug withdrawn</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Not present</td>
<td>Week:</td>
<td>-or-Duration</td>
<td></td>
<td>No</td>
<td>Moderate</td>
<td>Requires or prolongs hospitalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Months:</td>
<td>Days:</td>
<td></td>
<td></td>
<td>Severe</td>
<td>Caused a congenital anomaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Years:</td>
<td></td>
<td></td>
<td></td>
<td>Requires intervention to prevent permanent damage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unknown</td>
<td>Still Present</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unknown</td>
<td>Worsening</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>Yes</td>
<td>Present</td>
<td>Start date:</td>
<td>Name of medication:</td>
<td>Yes</td>
<td>Mild</td>
<td>Drug withdrawn</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Not present</td>
<td>/ /</td>
<td></td>
<td>No</td>
<td>Moderate</td>
<td>Requires or prolongs hospitalization</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stop date:</td>
<td></td>
<td></td>
<td>Severe</td>
<td>Caused a congenital anomaly</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-or-Duration:</td>
<td></td>
<td></td>
<td>Requires intervention to prevent permanent damage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days:</td>
<td></td>
<td></td>
<td>Still Present</td>
<td>Worsening</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Months:</td>
<td></td>
<td></td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Years:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>Yes</td>
<td>Present</td>
<td>Start date:</td>
<td>Name of medication:</td>
<td>Yes</td>
<td>Mild</td>
<td>Drug withdrawn</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>Not present</td>
<td>/ /</td>
<td></td>
<td>No</td>
<td>Moderate</td>
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<td></td>
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<td>Stop date:</td>
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<td>-or-Duration:</td>
<td></td>
<td></td>
<td>Requires intervention to prevent permanent damage</td>
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<td></td>
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<td></td>
<td>Days:</td>
<td></td>
<td></td>
<td>Still Present</td>
<td>Worsening</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Months:</td>
<td></td>
<td></td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Years:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pharmacy data (TSR 5)

**Adult Prescription Form**

<table>
<thead>
<tr>
<th>AMPATH#</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Name**

<table>
<thead>
<tr>
<th>Gender:</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Type:</td>
<td>Routine</td>
<td>PMTCT</td>
</tr>
</tbody>
</table>

**Check all that apply:**

- ARV Refill
- OI Refill
- Non-ARV Medications (flip)
- Initiation of ARV’s
- Regimen Change, if ticked, you must check one of the following options
  - Side Effects
  - Treatment Failure
  - TB Drug Interaction (during induction)
  - Pregnancy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Month Supply</th>
<th>Other</th>
<th>Pill Count</th>
<th>Dispensed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 2 3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Activities implemented

- Establishing a working area
Activities Implemented

- Training of staff
  - Biomedical research and biomedical responsible conduct of research
  - Comprehensive management of HIV infected patients
  - Study tools
  - Role playing of study procedures

- Recruitment and follow-up of participants

- Development and use of the Redcap database
Preliminary results

- Oct 2012 to Sept 2013
- KPPB forms (TSR 1)

<table>
<thead>
<tr>
<th>Suspected Drug</th>
<th>Number of SADR cases (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stavudine</td>
<td>191 (78.9)</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>27 (11.2)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>11 (4.5)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td>Abacavir</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>242</strong></td>
</tr>
</tbody>
</table>
Pie chart representation

KPPB reports

- Stavudine: 11%
- Zidovudine: 5%
- Nevirapine: 3%
- Tenofovir: 2%
- Efavirenz: 0%
- Abacavir: 79%

1/17/2014
Sampled 44 random charts (at least 4 charts per category)

- 642 reported symptoms
- 161/642 (25.1%) were related to medications over 139 follow up visits
  - 30 symptoms over 57 visits by peers
  - 131 symptoms over 82 visits by pharmaceutical technicians

For the same dates Open MRS records of the clinical encounter forms had 40 reported symptoms
Patient Interviews (TSR 3 and 4)

- All categories are full except for:
  - Children started on 1\textsuperscript{st} line 28/150
  - Children started on 2\textsuperscript{nd} line 5/50
Adult follow up interviews

Number of Visits

Percentage of Participants following up

TSR 3 and 4 Follow Up Interviews

1/17/2014
Children follow up interviews

TSR 3 and 4 Follow Up Interviews

Number of Visit

Percentage of participants following up

Child 1st Line
Child 2nd Line
Child Stable
There have been 583 cases of change in ART

<table>
<thead>
<tr>
<th>Cause of cART regimen change</th>
<th>Number of cases (percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SADR</td>
<td>389 (66.7)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>77 (13.2)</td>
</tr>
<tr>
<td>Drug-drug interactions (mostly Rifampicin)</td>
<td>41 (7.0)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Undocumented</td>
<td>50 (8.6)</td>
</tr>
<tr>
<td>Phasing out</td>
<td>22 (3.8)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>583</strong></td>
</tr>
</tbody>
</table>
Pie chart representation

Causes of change in ART regimen

- SADR: 67%
- Treatment failure: 13%
- Drug-Drug Interaction: 7%
- Pregnancy: 4%
- Phasing Out: 8%
- Unnnown: 1%

1/17/2014
Challenges and Lessons Learnt

National PV SADR forms
- Incomplete data – even after combining pharmacy data and Open MRS data (147 unreported cases [37.8%])
- Point person to complete and submit the forms

Routine clinical encounter forms
- Few symptoms reported
- In high volume HIV care programs, proper infrastructure has to be developed to document SADRs
- Needs to relay data to national PV program
Lessons Learnt

Patient Interviews

- Training the staff on HIV management and antiretrovirals enhanced the data collection
- Random sampling didn’t work for TSR 3 and TSR 4 therefore we changed the recruitment and enrollment strategy
- The interviews provided a platform to address other issues including disclosure, non-adherence and food – insecurity
- Disclosure of HIV status to children is occurring at a later age
Lessons Learnt

- Incentives and calling patients on their phones improved TSR 3 and TSR 4 follow up visits
- Patients preferred to call the study phone numbers for advice
- Medication errors

Pharmacy data
- Great system to flag changes in ART
- For complete picture - need to combine with other sources of data
Way forward

Publications

- Feasibility and ethics of implementing TSR approaches
- Evaluation of the implementation of the national pharmacovigilance forms at AMPATH
- Pediatric Pharmacovigilance: adverse drug reaction in children on HAART using a focused symptom screen form
Scale up and progress

- PV TB/Onc
- ART Adherence project
- Counterfeit drug detection
- Pharmacy Peer counseling
- Pharmacy Database SADR
Conclusion

- Task shifting to peers can be used to bridge the gap in healthcare provision and this will translate to increase in adverse drug reaction reporting.

- Modification of the approaches to suit different settings.
References

WHO fact sheet
accessed on the 20/Apr/2013

