KalaDrug-R

SOP for Retrospective Quarterly Cohort Analysis for patients treated for KA, from the improved Daily Record Register for Kala azar patients

Version January 2012

Tools required:

Daily Record Register for Kala azar patients
blank RQCA report form

1. Background

Retrospective Cohort Analysis (RCA) is a tool to measure treatment outcomes at program level (not on individual level) to see whether the program performs well. It has been validated and is used routinely for the evaluation of Tuberculosis treatment programs to see if the objectives for TB control are met (a minimum cure rate of 85% of newly detected cases of sputum smear-positive TB are needed to reduce and control the problem of acquired drug resistance[1]).

For leishmaniasis, such objectives have not been set (yet), but cure rates in phase 4 trials indicate that Miltefosine cures only 89 to 94% of cases (1). Calculating these outcome indicators in sentinel sites and in Reference Centers like KAMRC and BPKIHS - now that Miltefosine is used routinely - will allow to measure the rates of treatment failure and relapse, to compare in between regions and to monitor their evolution over time. This information will be essential for local District Health Offices to evaluate the efforts needed e.g. to improve adherence to treatment, as well as for RTAG to evaluate current treatment guidelines and adapt them when necessary.

Note that this RCA does not analyse drug efficacy but treatment program efficacy and that low cure rates do not necessarily mean that the drug is failing. For this, other analyses can be done on the data collected in the register, whereby outcomes need to be classified differently. This alternative analysis is not covered in this SOP.

2. Procedure

RCA can be easily done when the KA case register is correctly filled in.
1) Select the cases registered over the relevant 3 month period.

[1] TREATMENT OF TUBERCULOSIS: GUIDELINES FOR NATIONAL PROGRAMMES, third edition ©World Health Organization – Geneva, 2003

2) Count the total number of the KA cases registered and
3) Count the new cases only (registered in the *"new case"* column under the *"type of Patient"* heading).
4) Subdivide by treatment (MIL, AMPHO, …).

The **early outcomes** can be calculated as soon as the last person of the cohort has finished his treatment (so theoretically already 1 month after the end of the cohort period. Outcomes are mutually exclusive and correspond with the case definitions as proposed by TDR (2): Initial Cure, Non-Response (or failure), Default, Side-effects related switch (treatment stop because of Severe Adverse Events) and Death.

Transfer out is an additional option for patients initially registered in the records of one health structure, and transferred during the course of the treatment to another treatment facility, whereby early (and late) treatment outcome is unknown. This to avoid double reporting.

Final outcome is the patient's status six months after finishing treatment. As the patient is given an invitation to present him/herself after 6 months, the final outcome analysis may be done only after a period of passive waiting, followed by active tracing if he/she hasn't reported spontaneously. (Note that it may be sufficient to have an indirect contact reporting on the health status of the ex-KA patient: e.g. through a female health worker or ASHA, presenting at monthly DHO meetings or through a telephone contact with a household member or a neighbour).

A final outcome analysis of the cohort that started on 1st of January 2010 (up to March 31st) should thus be available at the earliest by October 28th (28 days + 6 months after the last patient from the cohort –provided he/she started treatment on March 31st and finished after 28 days, i.e. on April 28th). More realistically, given some delays for tracing patients, a final outcome report should be ready for this cohort by the end of the year (11 - 12 months after the start of the cohort.

Final outcomes are:
- in cases where the early outcome was **NOT** initial cure: the same as the outcome at that time i.e. *Non-Response*, *Default*, *Side-effects related switch* or *Death* (or transfer out)
- in cases where the early outcome had been *Initial Cure* at the time: final outcome options are then: *Final cure*, *Relapse*, *Death* or *Loss to follow-up* (2).

The outcomes of new cases are the main interest of the cohort analysis. Outcomes can equally be calculated in the same way, for other groups of patients i.e.:

PKDL cases,
Re-treatments after failure or relapse, and
Treatment switches after default or SAE

and for other drugs (in most of the re-treatments the drug of choice will be Ampho-B, but also here success rates are important to monitor).

For program managers, entering (copying) the daily KA register(s) in an excel sheet with "filter" options will make retrospective cohort analysis easy.

Late(r) treatment outcomes

In the current TDR guidelines, there are only 2 time points proposed for treatment monitoring e.g. at the last day of drug treatment and at six months after the last drug taken (2).
However, monitoring of treatment outcomes can be repeated at later time points using the same methodology and case definitions as the one used at 6 months.
According to the literature, most relapses after treatment are seen within 6 to 12 months after treatment (3-5). Most scientific publications however only report 6 months of outcome monitoring (thus risking underestimating the relapse rate). In patients re-presenting with VL symptoms late after the previous treatment, re-infection cannot be ruled out (even though cellular immunity is said to protect against re-infection (ref. Stanley & Engwarda 2007))
However, there are reports of a substantial number of relapses in the period of 6-12 months after treatment which justify longer systematic recording of outcomes – if not in routine conditions then certainly in sentinel sites.
For this reason, Kaladrug-R is also actively collecting treatment outcomes at 12 M post-treatment.

Reporting format

A reporting format has been developed, based upon the TB Retrospective Quarterly Cohort Monitoring (RQCM) Reporting.
Cohorts are defined by date of start of treatment: they include all patients initiated on VL treatment over a period of one trimester (January-March, April-June, July-September, or October-December), regardless of the date of end of treatment.

Given the fact that treatment duration with currently available anti-leishmanial drugs does not exceed 1 month, Quarterly Reports on the most recent cohort can be drawn one month after the closing of the cohort, i.e. as soon as early treatment outcome of every single person in the cohort has been collected (if need be after active tracing).

In practice, drawing reports for VL outcome can thus be scheduled on 4 time points in the year: February, May, August and November.

At the same occasions the second part of the report can be drawn, covering the late treatment outcomes of the patients in earlier cohorts and who have all reached 6 (or 12) months post treatment.

Cohort (Year/Trimester)	RQCM Report EoT Outcomes	RQCM Report 6M Treatment Outcomes	RQCM Report 12M Treatment Outcomes
2010/1 (Jan-March)	May 2010	November 2010	May 2011
2010/2 (Apr-June)	August 2010	February 2011	August 2011
2010/3 (July-Sept)	November 2010	May 2011	November 2011
2010/4 (Oct-Dec)	February 2011	August 2011	February 2012

See Annex : Calendar

Case definitions in cohort analysis

Reminder: *the formulas below only fit for cohorts including patients treated for the first time. Patients treated earlier should be excluded in advance, to avoid re-treatments of the same patient (as they would appear twice in the denominator)*

Cure rate: % of those started on drug treatment (i.e. included in the cohort), that obtain cure

Early cure rate: at end of treatment (d29)
Late cure rate: at 6 or 12M after end of treatment

$$\frac{\text{Number of cured}}{\text{Number of patients in the cohort}}$$

Defaulter rate (%): % of those started on treatment who did not return for their drug-collecting visits, or did not attend the last visit (end of treatment). High risk for relapse since incomplete treatment/adherence. Indicator of the quality of VL management

$$\frac{\text{Number of defaulters}}{\text{Number of patients in the cohort}}$$

Non-responders' rate (%): % of those started on treatment in which signs and symptoms persist of recur despite satisfactory treatment for more than two weeks

$$\frac{\text{Number of non-responders}}{\text{Number of patients treated for} \geq 2 \text{ weeks}}$$

Treatment failure rate (%): Of those started on treatment (and for whom treatment outcome is known), % that fail to cure (i.e. those who die during treatment, those who require treatment switch because of non-response or because of SAE, and those who relapse in the follow-up).

$$\frac{\text{Sum of (Deaths, Defaulters, Treatment Switch for SAE, NonResponse, Relapse)}}{\text{Number of patients in the cohort with available treatment outcome.}}$$

Treatment completion Rate (%):

The Regional Technical Advisory Group On Kala-azar Elimination put forward three key indicators for the elimination program[2]: Detection rate, Coverage rate of vector control and Treatment completion rate. This last one is defined as "percentage of cases of kala-azar who completed a full course of first-line drugs.

This is:

$$\frac{\text{\# patients in the cohort } \textit{minus} \text{ \# of deaths during treatment, defaulters, treatment switch because of SAE, treatment switch because of non-response…}}{\text{Number of patients in the cohort.}}$$

Practical procedures

Evaluation of treatment efficacy stands or falls with the quality of data collection in the register. This requires efforts from clinicians and data managers, but is above all an organisational matter: Clinicians, data managers and District Health Authorities must sit together to develop the most appropriate strategy to obtain the highest level of completeness of data. Different approaches are possible.

1. In order to obtain maximum adherence to the treatment prescribed and the punctuality for return visits, patients need to receive correct information on their illness (transmission, signs and symptoms, outcome if left untreated) and the treatment (duration, side-effects, strategies to cope with side effects),

- information needs to be adapted to the level of education and capacity of understanding.
- make use of the tools that have been designed by MoH for KA management: patient treatment card indicating duration of treatment, and dates for follow-up appointments.
- involve whenever possible a second person (relative), while providing the information above, so this person will help to supervise treatment adherence

[2] RTAG on Kala-azar Elimination, Report of the Third Meeting, Dhaka, Bangladesh, 8-11 December 2009, WHO 2010, SEA-CD-204

2. Ideally, people should return for their follow-up visits as planned. Make sure to collect maximum data on address and ways to contact the patient in order to be able to trace him in case he/she fails to come back. Tracing is very labour-intensive (but necessary), so responsibilizing the patient to return is worthwhile

3. Tracing can be done through the existing village health workers network(s). The District Health Office will play a crucial role in this as they make the link and coordinate and supervise the tasks of the health workers (monthly meetings). A training/ information session for the assigned network (VHW, ASHA) must be organised at the start of the project to explain the importance of treatment outcome monitoring and their role.

4. For the 6 (and 12) month treatment outcome monitoring, the data managers can draw up the list of patients who need to report to the clinic. This list can then be shared in advance with the DHO who can inform the village health worker concerned.

5. "Lost to Follow-up" is assigned to patients from whom no information could be found, i.e. after tracing. In some cases, patients classified as "Lost to Follow-up" at 6M, may be traced successfully at 12M. In such cases, the retrospective information on their condition at 6M may ultimately be recorded in the report/register under "comments" ; if relapse is reported at 12M, find out if when the relapse occurred (date) or at least whether the relapse was before the 6M timepoint (relapse at 6M) or after. Keep "LtFU" as the outcome of 6M (do not correct retrospectively).

The data collected in the KA register and reported in the RQCM are only relevant for decision making if they are complete. With only 50% of outcomes available, results of those 50% cannot be extrapolated to the whole cohort, as the other half may include much more deaths and failures than the ones for whom the information was easily collected.
Therefore **a data completeness rate of at least 80%** should be obtained, and all possible strategies should be tried –during the pilot phase- in order to obtain $\geq$ 90%. (No reference, this is a proposal).
Strategies used should be documented (costs, efforts, human and financial resources, time etc.) in order to compare cost-benefit of the interventions and recommend to other health districts.

Annexes: KA Register
Quarterly report Form
Calendar for reporting

SOP written on February 2010, bo
1st Update on December 2010 bo
2nd Updated in September 2011 bo
3rd Updated on March 2011 bo
4th Updated in February 2012 bo

Reference List

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2. TDR, SEARO. Indicators for monitoring and evaluation of the kala-azar elimination program. August 2010; p5-6.
3. Murray, HW. Progress in treatment of a neglected disease: visceral leishmaniasis. Expert Rev. Anti-infect.Ther.2004;2:279
4. Wijers, DJB. A ten years' study of kala azar in Tharaka (Meru District, Kenya). II Relapses. E.Afr.Med.J. 1971;48:551.
5. Nyakundi, PM, Wassuna KMA, Rashid JR, Gachichi GS, Mbugua J et al. Is one year follow-up justified in kala-azar post-treatment? E.Afr.Med.J. 1994;71:453.

Annex 3:

Calendar for quarterly Reports preparation

Timing	Reports:		
May 2010	EoT 2010/1		
August 2010	EoT 2010/2		
November 2010	EoT 2010/3	6M pT 2010/1	
February 2011	EoT 2010/4	6M pT 2010/2	
May 2011	EoT 2011/1	6M pT 2010/3	12M pT 2010/1
August 2011	EoT 2011/2	6M pT 2010/4	12M pT 2010/2
November 2011	EoT 2011/3	6M pT 2011/1	12M pT 2010/3
February 2012	EoT 2011/4	6M pT 2011/2	12M pT 2010/4
May 2012	EoT 2012/1	6M pT 2011/3	12M pT 2011/1
August 2012	EoT 2012/2	6M pT 2011/4	12M pT 2011/2
November 2012	EoT 2012/3	6M pT 2012/1	12M pT 2011/3
February 2013	EoT 2012/4	6M pT 2012/2	12M pT 2011/4
May 2013	EoT 2013/1	6M pT 2012/3	12M pT 2012/1
August 2013	EoT 2013/2	6M pT 2012/4	12M pT 2012/2
Etc.			