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Timing for Definitive Cure in Clinical Trials for Visceral Leishmaniasis

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ABSTRACT

Background: Visceral Leishmaniasis (VL) is a parasitic neglected tropical disease, endemic in developing countries. Treatment outcomes in VL clinical trials are measured at two time points: a) initial cure at end of treatment (EOT) and b) definitive cure (DC) measured commonly at six months post EOT. Additional assessment is commonly conducted at either one or three months post EOT for patient monitoring. This paper investigates justification for shortening of the six month follow-up time point in the assessment of DC. **Methods:** A three state Markov model has been applied to estimate the transition probabilities for DC using data from a phase III clinical trial conducted in East Africa to compare the safety and efficacy of three different treatment regimens. At baseline all patients were untreated but their status changed to either treatment failure (TF) or success (TS) at EOT, month 3 or 6 follow-up with TF considered as an absorbing state. **Results:** Conditional on a patient ever having a TS, 98.5% of observations have a TS outcome at the next visit while that of ever having a TF is 61.4%. From the transition probabilities, approximately 1% of patients change cure status between month 3 and 6. Overall, there was high stability for the treatment outcomes (>97%). **Conclusion:** Advantages of shortening follow-up time include a possible reduction in loss to follow-up and time to availability of effective new treatments. Limitations to be addressed in simulation studies include the possibility of false negative results and differences in relapse rates between treatment regimens.

***Keywords*—** Timing, Definitive Cure, Visceral Leishmaniasis, multi-state models**.**

INTRODUCTION

Clinical trials for Visceral Leishmaniasis (VL) are conducted primarily to identify treatments which are safe and efficacious in the management of patients suffering from VL, a neglected tropical disease endemic in a number of developing countries(1). The cure for VL is assessed mostly by use of an invasive and painful process at the end of treatment (EOT) or 6 months after treatment. In certain instances assessment is also done at either 1 or 3 months after treatment (Figure 1).

In VL, the timing for definitive cure is 6 months after treatment which has always been a critical time point in determining final cure in most clinical trials (2-6).

One of the challenges with long follow-up in VL clinical trials has been loss to follow-up. With such long follow-up also comes the challenge of being able to determine at what time point a patient is considered to either have re-infection or relapse if confirmed as treatment failures.

In terms of clinical trial conduct, longer follow-up could be inefficient and uneconomical when thinking of the development of new or cheaper treatments for VL(7). This therefore calls for a review of available clinical trial data to investigate whether the long follow-up time is justified or can benefit from a detailed study with several time points for purposes of determining one single time point before 6 months to assess definitive cure.

Our interest in this timing for definitive cure is motivated by the fact that a) longer follow-up may be a contributing reason to loss to follow-up in most VL trials. In terms of implementation of treatments in normal settings, it makes sense to have treatments which would not inconvenience patients from running their daily lives upon successful completion of treatment administration and this is the case in phase IV trials (pharmacovigilance), b) there is a possibility that re-infection may occur over the long follow-up period.

In the two trials conducted by the Leishmaniasis East Africa Platform (LEAP) (3,8), a total of 24 patients out of 270 (9%) were lost to follow-up by the 6 month follow-up time point in the first case while lost to follow-up was 5% in the second (50 patients out of 972 enrolled).

We have therefore sought to establish if significant treatment outcome differences exist between two follow-up time points (month 3 (M3) 3 & M6) and determine how much M3 outcomes are predictive of the M6 outcomes and if there is need to review when definitive cure should be assessed.

Besides the standard calculation of proportions based on exact treatment outcomes, we have also considered multi-state models which are probability models that describe the random movement of a subject between a series of states in continuous/discrete time.

Nowhere has multi-state models been used in VL characterization but with an interest in estimating the transition probabilities in VL, we have adopted the multi-state model by looking at different disease states within the treatment and management framework for VL.

Our interest was specifically on success or failure as treatment outcomes (states) at discrete time points; EOT, M3 & M6 follow-up (Figure 1).

The transition probability from state S_i to S_j is written as

$P_{ij}\ n = P\ X_{n+1} = S_j\ |X_n = S_i$ i.e, given the present state of the system, $X_n = S_j$ the future of the system is independent of the past. If the Markov property holds and the transition probabilities do not depend on n, we say that the process is a (time) homogeneous Markov Chain(9).

Materials and Methods:

Data used comes from the following trials:

- LEAP 0104 (8) and LEAP 0106 (5,10).

Definition for follow-up:

The day of follow-up assessments has been calculated from EOT.

- A visit is considered to be at EOT (end of treatment) if it occurs on EOT (±2 day)
- A visit is considered to be at M3 (day 90) if it occurs on day 90 (±14 days)
- A visit is considered to be at M6 (day 180) if it occurs on day 180 (±30 days)

For purposes of this analysis, anything falling outside the window period above was classified as missing and has been excluded from the final analysis. The extent of missingness from the above criteria has been produced to help in understanding gaps arising from such trials.

Figure 1: Timing of Cure Assessment for VL

Modeling transitions between States:

In modeling the transition between two states, 1 (treatment success) and 2 (treatment failure), a first order autoregressive model (AR(1)) has be used. An AR(1) model for the probability that an individual j is in state 1 at time t, P_n is

$$\log\left(\frac{p_{tj}}{1-p_{tj}}\right) = \alpha + x_{tj}\beta + \gamma\, y_{t-1\,j} + u_j$$

Where

α is an intercept term

γ is the effect of the state occupied at $t-1$ on the log odds of being in state 1 at t

$u_j \mapsto N(0, \delta_u^2)$ is an individual specific random effect.

We model $p_{tj} = Pr\ (state\ 1\ at\ start\ of\ t)$

$= Pr\ (Y_{tj}=1) = \Pr(y_{tj}=1)$

Suppose we fix $x_{tj}=0$ *and* $u_j=0$

The probability of moving from state 1 to 2 is

$$\Pr(y_{tj}=0 \mid y_{t-1j}=1) = 1 - \Pr(y_{tj}=1 \mid y_{t-1j}=1)$$
$$= 1 - \frac{\exp(\alpha+\gamma)}{1+\exp(\alpha+\gamma)}$$

While the probability of moving from state 2 to 1 is given by

$$\Pr(y_{tj}=1 \mid y_{t-1j}=0) = \frac{\exp(\alpha)}{1+\exp(\alpha)}$$

Since same individuals can contribute observed time at risk to more than one state, observations made relate to the number of events and total time at risk rather than the number of individuals(11).

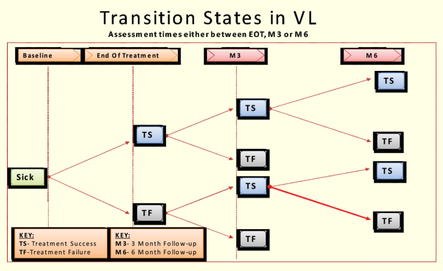

Figure 2: VL transition states

Predictive Model

We have come up with a probability value, $P_{1,2}$ (and its 95% confidence interval) defined as the probability of no change in cure status between two time points 1, 2 (i.e EOT and M3 or M3 and M6) to determine how much of M6 outcomes can be predicted by M3 outcomes or M3 by EOT outcomes.

Where $p_{1,2} = \begin{cases} cure(T_{1,2}) \\ cure(T_{1,2}) \end{cases}$

In coming up with $P_{1,2}$, we have assumed treatment success (clinical cure) by M3 in instances where parasitology was not done. This is because parasitology was only being done at these time point when clinically indicated.

RESULTS:

Treatment Outcomes: LEAP 0104 Multi-state Model

Table 1: Person visits by treatment outcome

Outcome	Overall	Between	Within
Treatment success	1072 (98%)	366 (97.9%)	98.5%
Treatment failure	22 (2%)	22 (5.1%)	61.4%
Total	**1094 (100%)**	**388 (103.7%) [374]**	**96.4%**

There were 1072 person visits of data in which the treatment outcome was a success and 22 person visits where it was a failure (2% of our data). 366 patients ever had a treatment success while 22 ever had a treatment failure with a total of 388 ever having either. In our data set however, we only have 374 patients which means that there were those who sometimes had successes and failure at other times.

Conditional on a patient ever having a success, 98.5% of their observations had a success outcome, similarly, conditional on ever having a failure, 61.4% of a patients observation had a failure.

Table 2: Transition probabilities

Outcome	Treatment success	Treatment failure	total
Treatment success	706 (99%)	7 (1.0)	713 (100)
Treatment success	7 (100%)	0	7 (100)
Total	**713 (99.0%)**	**7 (1.0%)**	

At each visit, some 99% of treatment success in the data remained treatment successes at the next visit with the other 1% being failure at the next visit.

Standard predictions:

Among the 359 patients who had cleared parasites (negative) by EOT, only 5 (1.3%) became positive by the M3 follow-up assessment. This implies that, there was a 98% probability of a patient with no parasites at EOT remaining parasite free by M3 follow-up while of the 369 patients who had cleared parasites (negative) by M3, only 2 (0.5%) became positive by the M6 follow-up assessment implying that there was a 99% probability of a patient with no parasites at M3 remaining parasite free by M6 follow-up (Table 6).

Characteristics of patients who change cure status: End of Treatment to Month 3

- Very high parasite counts at baseline with exception of one case (count of 1x 10^6)
- Very large spleens at baseline (>6cm) which either reduced marginally or increased in size by the M3 assessment time point.

Characteristics of patients who change cure status: M3 to M6

- Look like relapse cases as they were both negative by EOT as well.
- Marked reductions in spleen sizes.

Treatment Outcomes: LEAP 0106
Multi-state Model

Table 3: Person visits by treatment arm

Outcome	Overall	Between	Within
Treatment success	127 (98.5%)	44 (97.8%)	98.9%
Treatment failure	2 (1.5%)	2 (4.4%)	75.0%
Total	**129 (100%)**	**46 (102.2%) [n=45]**	**97.8%**

There were 127 person visits of data in which the treatment outcome was a success and 2 person visits where it was a failure (1.5% of our data). 44 patients ever had a treatment success while 2 ever had a treatment failure with a total of 46 ever having either.
Conditional on a patient ever having a success, 98.9% of their observations had a success outcome; similarly, conditional on ever having a failure, 75% of a patient's observation had a failure.

Table 4: Transition probabilities

Outcome	Treatment success	Treatment failure	Total
Treatment success	83 (98.8%)	1 (1.2%)	84 (100%)
Treatment failure	-	-	-
Total	**83 (98.8%)**	**1 (1.2%)**	

At each visit, some 98.8% of treatment success in the data remained treatment successes at the next visit with the other 1.2% being failure at the next visit.

Standard predictions:

Among the 44 patients who had cleared parasites (negative) by EOT, only 1 (2.2%) became positive by the M3 follow-up assessment indicating a 98% probability of a patient with no parasites at EOT remaining parasite free by M3 follow-up while among the 44 patients who had cleared parasites (negative) by M3, only 1 (2.2%) became positive by the M6 follow-up assessment implying a 98% probability of a patient with no parasites at M3 remaining parasite free by M6 follow-up.

Characteristics of patients who change cure status: End of Treatment to Month 3

- Increased spleen size between the two time points (3 to 5 cm).
- Reduction in its spleen size from 7cm to 2cm.

Characteristics of patients who change cure status: M3 to M6

- Increased spleen size between the two time points and looks like a relapse case.

Table 5: Assessment days: LEAP 0104

	EOT	Day 90	Day 180
Seen within window period	925	532	612
Seen outside window period	22	249	317
Parasitology done	924	532	612
Parasitology not done	1	196	0
Received rescue treatment	61	9	15

Table 6: LEAP 0104 treatment outcomes: EOT to M3

End of treatment	Day 90 (3 months) follow-up		
Negative	Negative	354[a]	98% [96.8 - 99.5]
	Positive	5[b]	
Positive	Negative	0	100% [78.2 - ¥]
	Positive	15[c]	
Day 90 (3 months) follow-up	**Day 180 (6 months) follow-up**		
Negative	Negative	367[d]	99% [98.1 - 99.9]
	Positive	2[e]	
Positive	Negative	1[f]	80% [28.2 – 99.5]
	Positive	4[g]	

[a]A total of 8 cases received rescue treatment; [b]All the 5 patients had received rescue by M3; [c]Eight patients were given rescue treatment; ¥One sided 97.5% confidence interval d A total of 14 cases received rescue treatment;
[e]All the 2 patients had received rescue by M6; [f]1 patients was given rescue treatment; [g]All the 4 patients were

Table 7: Assessment days: LEAP 0106

	EOT[a]	Day 90	Day 180
Seen within window period	121	60	81
Seen outside window period	0	40	32
Parasitology done[b]	121	60[c]	81
Parasitology not done[b]	0	0	0
Received rescue treatment[b]	36	1	2

a End of Treatment (day 30)
b Among those seen within the window period
c Assumed to be parasite free if parasitology is not clinically indicated

Table 8: LEAP 0106 treatment outcomes: EOT to M3

End of treatment	Day 90 (3 months) follow-up		
Negative	Negative	43[a]	98% [88 - 99]
	Positive	1[b]	
Positive	Negative	0	-
	Positive	1[c]	
Day 90 (3 months) follow-up	**Day 180 (6 months) follow-up**		
Negative	Negative	43[d]	98% [88 - 99]
	Positive	1[e]	
Positive	Negative	0	-
	Positive	1[f]	

[a]A total of 2 cases received rescue treatment; [b]One patients had received rescue by M3; [c]1 patients was given rescue treatment; [d]A total of 2 cases received rescue treatment; [e]One patients had received rescue by M3; [f]1 patients was given rescue treatment

DISCUSSION:

One of the interesting results from this review is the significant number of patients who are not being assessed within the expected follow-up time points (Table 6 & Table 8).

From these results, it is clear that there are very few cases in which changes in treatment outcomes occur between M3 and M6 follow-up time points. The 95% confidence interval on no change in cure status between M3 and M6 has a probability of between 98% & 99.9%. Under very limited circumstances (about 0.5%) do patients change cure status between M3 and M6 (Table 5 & Table 6). It is therefore possible to predict this limited change based on other patient characteristics like increase in organ size (e.g spleen or liver) after cure.

In terms of transition probabilities from the multi-state model, the change in treatment outcomes between visits is just about 1% in-case of treatment success at the first time point. The treatment outcomes also have high overall stability (>97%) as such can be relied on to form the basis for a review of the follow-up time point in the assessment of definitive cure for VL.

Generally, few patients changed their cure status between EOT, M3 & M6 follow-ups with those changing from success to failure all having slightly higher spleen sizes at the points they are declared failures. Nearly all patients who become successes after failure had received rescue treatment and just a few who did not receive any rescue (considered slow responders) had significant reduction in their spleen sizes.

Due to challenges with patient follow-up, only a third of the data set have been used in this analyses but this is assumed to be representative of the patient population of VL trials conducted in East Africa.

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