



“Efficacy trials of Lassa Therapeutics: endpoints, trial design, site selection”

WHO Workshop

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1. Introduction

Lassa fever (LF) is a zoonotic disease associated with severe and potentially fatal haemorrhagic illness caused by Lassa virus (LASV). LF has been shown to be prevalent in many West African countries, such as Benin, Ghana, Guinea, Liberia, Mali, Nigeria, and Sierra Leone. Four lineages of LASV were defined, based on genetic variation. In these countries, both sporadic cases and prolonged outbreaks of the disease are observed. LF is mainly transmitted through contact with infected *Mastomys natalensis*, a widespread rodent species in West Africa, and through food and items contaminated by those rodents. The virus can also be transmitted, to a lesser extent, by person-to-person contact. LF occurs in all age groups and both sexes and is associated with a broad spectrum of clinical manifestations. Symptoms of LF are varied and non-specific, making clinical diagnosis often difficult.

Hundreds of LF cases are estimated to occur yearly in West Africa. However, surveillance is inadequate to determine the true incidence of the disease and good epidemiological data is needed to better define the proportion of at-risk populations as well as endemic, hyper-endemic, and epidemic areas. About 80% of people who become infected with Lassa virus have no symptoms. 20% of infections result in severe disease, where the virus affects several organs such as the liver, spleen and kidneys. The incubation period of Lassa fever ranges from 6–21 days. The onset of the disease, when it is symptomatic, is usually gradual, starting with fever, general weakness, and malaise. After a few days, headache, sore throat, muscle pain, chest pain, nausea, vomiting, diarrhoea, cough, and abdominal pain may follow. In severe cases facial swelling, fluid in the lung cavity, bleeding from the mouth, nose, vagina or gastrointestinal tract and low blood pressure may develop. Clinical diagnosis is often difficult, especially early in the course of the disease. LF is difficult to distinguish from other viral haemorrhagic fevers such as Ebola virus disease as well as other diseases that cause fever, including malaria, shigellosis, typhoid fever and yellow fever. Lassa virus infections can only be diagnosed definitively in the laboratory using RT-PCR, ELISA, Antigen detection tests, or virus isolation. None of those tests are currently licensed. Early supportive care with rehydration and symptomatic treatment improves survival. Ribavirin has been widely used off-label to treat patients with LF based on the results of one clinical study performed in Sierra Leone in the 80's. Lastly, there is no licensed vaccine.

In early 2018, Nigeria has witnessed an unprecedented LF outbreak, whereby the usual annual observed LF burden has been concentrated into one trimester. From 1st January to 29th April 2018, a total of 1878 suspected cases have been reported from 21 states. Of these, 420 were confirmed positive.

The endemicity of LASV in West-Africa and the occurrence of LF outbreaks have underscored the need to develop Lassa therapeutics. The WHO R&D Roadmap of LF notably identifies the following strategic goals:

1. more fully evaluate ribavirin for treatment of Lassa fever and determine the appropriate role of ribavirin in clinical trials of new therapeutics.
2. develop, evaluate, and license new and improved affordable therapeutic agents for treatment of Lassa fever and prevention of Lassa fever-associated sequelae, as well as for PrEP/PEP to prevent LASV infection, for the multiple LASV lineages.

Based on those goals, WHO convened on April 2018 a group of about 30 experts in epidemiology, regulatory, preclinical and clinical trials, in a workshop on planning for Lassa therapeutics efficacy trials. The workshop aimed to define generic principles on how to best design, conduct and analyse therapeutics trials against LF, based on the available scientific evidence as well as on lessons learned from the public health response to LF outbreaks.

According to the R&D Blueprint processes, conclusions of the R&D Roadmap of LF and a WHO Lassa therapeutic Target Product Profile (DRAFT) were expected to help inform therapeutic evaluation decisions during the workshop. Participants reviewed available evidence on Lassa epidemiology and therapeutic candidates, identified and discussed methodological options to evaluate therapeutics, regardless of the product, and agreed on some preliminary recommendations. Of note, post-exposure prophylaxis was excluded from the scope of the workshop.

It was recognised both that the preliminary recommendations are likely to evolve as new evidence is generated and also, they must be tailored to the social and cultural context of affected communities.

2. Context to Lassa therapeutics evaluation

Preliminary considerations to the conduct of a therapeutic trial.

Research has increasingly been a norm in responding to outbreaks of infectious diseases. The research response must be fully integrated in the broader control efforts and cannot be performed at the expense of the control efforts. For instance, during the 2018 Nigeria Lassa outbreak, a series of outbreak control measures were implemented, coordinated at the national level by Emergency Operation Centre. Control measures include enhanced epidemiological surveillance, improved case management and IPC, contact tracing, risk communication and community engagement strategies. In Nigeria, there are currently three laboratories equipped with RT-PCR to detect LASV and there are three Lassa treatment centres located in the three most affected states. In Nigeria, where clinicians have timely access to a RT-PCR results of LF patients, the diagnostic algorithm helps inform the treatment initiation, continuation and patient discharge. Expansion of laboratory capacity will help harmonize the different treatment strategies across the different Lassa treatment centres. National authorities are coordinating efforts towards the expansion of laboratory and case management capacity in an effort to improve access to testing and care in the affected communities and in a context where new diagnostic tools become available. The above public health response elements need to be considered in the design of a LF therapeutic trial.

There is currently no licensed Lassa therapeutics: there are at least 12 Lassa therapeutic candidates (new or repurposed molecules) currently identified in the pipeline.

Lassa therapeutic approaches include nucleoside analogues, entry inhibitors, and biologics (e.g. monoclonal antibodies). Several candidate therapeutic have shown to be safe, immunogenic and effective in preventing death and reducing viremia in a variety of animal models (e.g. guinea pigs, marmosets, cynomolgus macaques, ...) in various experimental set-ups with more or less predictive value for humans. Of note, the majority of the animal challenge studies were conducted using the LASV Josiah strain, a strain that was isolated in the 70's in Sierra Leone, that is not known to circulate nowadays, and that is genetically diverse to some of the LASV strains that are currently circulating.

The LF therapeutic TPP suggests that it is expected that Lassa therapeutic should have a good safety and toxicity profile, also in special populations such as children, as well as in pregnancy and lactation, who have a particular high LF burden. However, except for ribavirin, there is currently no safety data of any Lassa therapeutics at doses expected to be used to treat LF in humans.

Ribavirin has been widely used off label to treat against LF and other viral haemorrhagic fever diseases. Ribavirin is a guanosine analogue and broad-spectrum antiviral drug. The exact mechanism of action is unknown but the drug interferes in the DNA-RNA intracellular synthesis, inhibits protein synthesis and consequently viral replication. It is licensed by FDA for treatment of Respiratory syncytial virus (RSV) and Hepatitis C virus (HCV). Drug supply to affected countries has not been transparent and there are uncertainties regarding the quality of the drug.

The justification of the use of ribavirin is mainly based on one RCT study conducted in the 80's, that concludes on the efficacy of ribavirin in treating Lassa fever patients ¹. This was the only RCT designed to evaluate ribavirin in humans.

3. The need to generate reliable evidence on ribavirin efficacy to treat against LF

A preliminary systematic review of the efficacy of ribavirin in treating LF patients, presented at the workshop, suggests that:

There is no randomized evidence on the efficacy of ribavirin in treating Lassa Fever patients.

The clinical diagnosis of Lassa fever was not confirmed by laboratory testing according to currently acknowledged standards. It can therefore not be ruled out that non Lassa virus-infected patients were included in the study and their analyses. Although participants in the McCormick study were randomly allocated to receive either ribavirin i.v. or convalescent plasma, the efficacy of ribavirin versus placebo was assessed using a retrospective control group. The convalescent plasma group does not provide an appropriate comparison group to evaluate ribavirin efficacy, since it is also an unproven intervention, and hence neither its efficacy nor safety are known, which means that use of convalescent plasma could have improved or worsened patient outcomes. Therefore, the identified RCT must be regarded as an observational retrospective cohort study, with respect to the investigation of efficacy of ribavirin.

Evidence of ribavirin efficacy in treating the included Lassa fever patients was only shown in a subset of patients and when treatment is initiated within 6 days after onset of symptoms.

Efficacy was only seen in the subgroup of participants with AST > 150 U/L, a biomarker that predicts kidney failure and was most pronounced if treatment was started early after symptom onset, i.e. within 6 days. No benefit in terms of improved survival rates was demonstrated in other patients. However, the current practice is to use ribavirin in all patients (even with AST < 150 U/L). Additional methodological concerns potentially leading to critical bias suggest that the conclusions of this trial should be regarded with caution.

In addition, LF case reports are available from 5 other papers published in the scientific literature, which suggest that time from onset of illness to initiation of care is a prognostic factor for the clinical outcome. However, mortality appears unchanged if ribavirin i.v. is given later than 6 days after symptom onset.

Therefore, given the uncertainties of the evidence on ribavirin i.v. efficacy to treat LF and its risk-benefit profile in a context where promising molecules are being developed, and also given its costs, participants underscored the need to investigate the efficacy and safety of ribavirin and to generate randomized evidence on ribavirin efficacy. The approach on how to evaluate ribavirin will be further discussed in the next section but importantly, the need to

¹ McCormick, Joseph B., Isabel J. King, Patricia A. Webb, Curtis L. Scribner, Robert B. Craven, Karl M. Johnson, Luanne H. Elliott, and Rose Belmont-Williams. "Lassa Fever." *New England Journal of Medicine* 314, no. 1 (January 2, 1986): 20–26. <https://doi.org/10.1056/NEJM198601023140104>.

generate randomized evidence on ribavirin efficacy has strong implication on a Phase 2b/3 trial design and notably implies the definition of a trial comparator group whereby participants would be randomly allocated to receive the best supportive care without ribavirin. The perspective of defining such comparator group in the context of a clinical trial would need to be further discussed with the clinicians implementing the study, because ribavirin is perceived as part of the current standard of care. Nevertheless, the best supportive care provided in the context of a therapeutic trial may be more effective than the current standard of care to treat LF, given the potentially added medical and technical resources within a trial. Lastly, it was also agreed a systematic review of ribavirin efficacy from animal data needs to be done to complement the body of evidence.

More generally, it was recognized that an evidence-based evaluation is required to define appropriate and optimal standard of care for LF and to inform the scientific community of the quality of evidence. Given the need to accelerate clinical development and the limited incidence, there is a need to prioritize scientific questions that can be answered by animal models and clinical trials and phase 1 and 2 studies are essential in informing such prioritization.

3. Trial design considerations

It was expected that the WHO draft TPP for Lassa therapeutics (DRAFT) would inform workshop participants in the rationale of defining trial design elements.

3.1 Clinical endpoints selection

Mortality should be the primary endpoint of a Phase 2b/3 Lassa therapeutic trial.

The definition of primary endpoints should also be supportive of the public health objectives outlined in the TPP for Lassa therapeutics. Participants agreed that the primary objective of the study should be to determine the efficacy and safety of treatment with ribavirin i.v. (and potentially another drug) in reducing mortality due to confirmed LF disease.

Provided that LF cases are diagnosed and treated earlier on, with the means of new diagnostic tools that would be made available and suitable to detect LF cases early (ideally before symptoms appear), disease progression could be considered as a co-primary endpoint. In the absence of such ability to detect and initiate treatment early, progression to severe disease should be considered a secondary endpoint. Viral load trends estimated by RT-PCR could also help distinguish between mild and severe LF cases and could be also serve as a secondary endpoint.

3.2 Study population and site selection

Adults and children, including pregnant women, should be included in the study population of a Phase 2b/3 Lassa therapeutic trial

LF affects the general population at all ages and considerations should also be given to the inclusion of pregnant and lactating women, and other special populations depending on the

risk-benefit analysis on a given LF candidate therapeutic in those populations. All patients that meet the case definition for LF confirmed case should be included.

Currently, except for ribavirin, there is no toxicity or safety data of any LF therapeutic in humans. Dose-escalation Phase 1 and Phase 2 studies are needed to assess the safety profile in healthy adults and special populations, including immunocompromised people.

The need for a multi-centre approach

Given the low incidence of LF, there is a risk that incomplete results from underpowered trials may be misleading to decisions-makers. A multi-site approach under a “Master Protocol” may be required to increase the chance of including groups with a high incidence of LF disease, as well as providing an opportunity to evaluate treatment efficacy across different populations. Multiple seasons may be required to accumulate enough evidence as well. If the trial does not achieve the targeted number of events in the first season, the study must remain blinded to allow for further data collection. If the above is not possible, then a standard meta-analysis could be performed by pooling results from multiple studies.

A multi-site trial would require standardization of concepts (e.g. same master protocol, LF case definition, standardized comparator), fit-for-purpose instruments (e.g. standardized laboratory assays) used in the trial. LASV strain would also need to be sequenced if sites exist in areas with different lineages.

3.3 Randomization and comparator

There is a need for randomization

The clinical spectrum of LF and the time from onset of LF illness to initiation of care are extremely variable. In particular, time from onset of LF illness to initiation of care appears as an effect modifier for any treatment as would be variation in supportive care. Furthermore, there are heterogeneities in the standard of care provided across Lassa treatment centres although efforts towards the definition of a standardized treatment strategy against LF are ongoing. In settings where the timing and nature of supportive care vary, there is a need for randomized stratification by centre to better understand the true effect of an intervention.

Time from onset of LF illness to initiation of care, severity of LF cases at presentation, and other effect modifiers and confounding factors need to be accounted for in the analysis.

Factorial trial designs should be considered when there is reasonably evidence that a combination of drugs may be synergistic or additive and when the safety profile of combining two drugs has been established and is acceptable for use in humans.

The recognition that a single drug may not be effective in treating an acute viral disease such as LF, and the potential drug synergies or additive effects may point out to the need to consider a combination of drugs in treating LF. Lessons learned from HIV drug development highlight such approach. Under the above circumstances, a factorial design is the most efficient approach to answer several questions with one trial and consists in four arms where participants are randomized (1:1:1:1) to receive either best supportive care, ribavirin (+ the best supportive care), drug X (+ the best supportive care), or a combination of ribavirin and drug X (+ the best supportive care).

Prior to that, synergistic effects need to be investigated, first *in vitro*, then in blinded randomized and well-controlled non-human primate studies with an appropriate dose and

standard of care before being considered for clinical studies. Upon an acceptable risk-benefit profile in animal models, Phase 1 and 2 clinical studies are also required to establish the safety profile of the combination of both drugs in humans and to establish the appropriate dosing regimens, and to identify potential biomarkers that could be exploited in Phase 3.

If the conditions to run a factorial design are not fulfilled, a 1:1:1 individually-randomized trial should be conducted to evaluate ribavirin and another drug.

in this trial, participants would be randomized to receive either best supportive care, ribavirin i.v. (+best supportive care), or drug X (+best supportive care). Drug X safety, toxicity and dosing regimen should be first investigated as well as well-controlled *in vitro* and animal models would help prioritize the most appropriate candidate Drug X for evaluation.

Adaptive elements would also be acceptable (for example, dropping a poorly performing study arm early, if several drugs are being tested in the same trial), but all go/no go decisions need to be established in advance based on a sound statistical analysis plan. Dropping a study arm following an interim analysis typically occurs if the drug has been shown to do significant harm.

If a drug X is not available for testing, then a 1:1 RCT testing ribavirin against the best supportive care could be envisaged although this would be less efficient than looking at two different drugs and potentially its combination against a comparator.

The above trials are open-label given the fact that ribavirin is given intravenously although the use of a placebo should be prioritized whenever possible.

4. Next Steps

A series of collaborative steps to continue to advance the discussions were outlined and agreed upon. It is anticipated that the steps will be implemented in close collaboration with the workshop participants and other experts in the community as appropriate.

- a) **Developing an annotated generic protocol for Lassa therapeutic efficacy trials, based on preliminary design consensus.** The generic protocol will be developed with inputs from all participants, and it will be published on the WHO website for public consultation by Fall 2018. A study synopsis will first be circulated. It is anticipated that candidate therapeutic developers and industry representatives will be informed of the consultation process and invited to provide their perspectives.
- b) **Finalize a TPP for Lassa therapeutic in consultation with partners.** A WHO therapeutic Target Product Profile is needed to provide aspirational guidance to drug developers, and will be informed by regulatory expectations and by technological feasibility.
- c) **Continue efforts towards standardization and harmonization of core clinical variables and clinical case management.** A case definition of LF that accounts for the distinction between mild and severe LF cases will be developed. A WHO clinical management guide to treat LF that includes a definition of a standard of care will be finalized and its implementation will be promoted across affected countries.
- d) **Support research capacity and plan for clinical trials.** WHO and partners will continue to promote research collaboration with relevant groups, to gain knowledge on LASV transmission, and prepare for a multi-site approach for LF therapeutic evaluation in concertation with the national authorities of the affected countries, including regulatory authorities and ethics committees. WHO will support expansion of laboratory capacity and training of healthcare workers to prepare for clinical research.