Strengthening Bolivian Pharmacovigilance system: new therapeutic strategies to improve health of Chagas Disease and Tuberculosis patients

RUNNING TITLE: Strengthening Bolivian Pharmacovigilance system

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1 **ABSTRACT**

2 Introduction: Chagas disease (CD) and Tuberculosis (TB) are important health problems in

3 Bolivia. Current treatments for both infections require a long period of time, and unwanted

4 drug-related adverse events (ADRs) are frequent.

5 Purpose: This study aims to strengthen the Bolivian Pharmacovigilance system, focusing on CD

6 and TB.

7 Methods: A situational diagnosis of Pharmacovigilance in the Department of Cochabamba was

8 performed. The use of a new Local Case Report Form (CRF) was implemented, together with

9 the CRF established by the Unidad de Medicamentos y Tecnología en Salud (UNIMED), in

10 several health care centers. Training and follow-up on drug safety monitoring and ADR

11 reporting was provided to all health professionals involved in CD and TB treatment. A

12 comparative analysis of the reported ADRs using the CRF provided by UNIMED, the new CRF

13 proposal, and medical records, was performed.

14 Results: Out of the total patients starting treatment for CD, 35,35% suffered ADR according to

15 the information collected in the medical records, and 25% of them were classified as

16 moderate/severe (MS) types. Only 51,43% of MS ADRs were reported to UNIMED. Regarding

17 TB treatment, 9,89% of the total patients suffered ADR, 44% of them were classified as MS,

18 and 75% of MS ADRs were reported to UNIMED.

19 Conclusions: The reinforcement of the Bolivian Pharmacovigilance system is an ambitious

20 project that should take a long-term perspective and the engagement of national health

21 workers and other stake holders at all levels. Continuity and perseverance are essential to

22   achieve a solid ADR reporting system, improving patient safety, drug efficacy and adherence to

23   treatment.

1. INTRODUCTION

25   Chagas disease (CD), caused by the parasite *Trypanosoma cruzi (T. cruzi)*, is one of the main

26   health problems in Latin America. *T. cruzi* infection has been declared as a major public health

27   issue in the region, affecting approximately 6 to 7 million people worldwide. Bolivia is the

28   country with the highest prevalence and incidence of CD. In addition, travel and immigration

29   patterns have increased the relevance of *T. cruzi* infection outside of endemic areas [1-3].

30

31   CD is recognized as one of the 17 neglected tropical diseases (NTDs), for which pharmaceutical

32   industry does not assign resources to invest in research and development of new drugs.

33   Approved drugs for treatment of *T. cruzi* infection (beznidazole and nifurtimox) are complex,

34   and unwanted drug-related adverse events (ADRs) are frequent. The onset of the ADR is one of

35   the main causes that lead to patient abandonment, resulting in therapeutic failure or

36   ineffective treatment [4-9].

37

38   Tuberculosis (TB) is another important health problem in Bolivia, where the prevalence and

39   incidence of the disease is high compared to other South American countries. TB treatment

40   involves the combination of several drugs over a long period of time, with high frequency of

41   ADRs, which compromise the effectiveness of treatment. In addition, resistance to current

42   drugs has been increasing during the last years [10-12].

43

44   In the management of CD and TB, poor adherence to treatment continues to be another

45   challenge to face. Factors contributing to poor medication adherence include lack of follow-up

46   protocols during treatment, and toxicity of the drugs. Nevertheless, with an adequate

47   management of the drugs, most of patients are able to finish treatment even in case of ADRs,

48   which in CD are usually mild and well controlled with symptomatic treatment. Close medical

49   follow-up, monitoring ADRs and implementation of robust Pharmacovigilance systems are

50   essential factors to avoid patient abandonment and achieve therapeutic success [13-17].

51

52   In the current context of CD and TB in Bolivia, strengthening the Bolivian Pharmacovigilance

53   system is proposed as a key issue to reinforce therapeutic strategies. To implement a strong

54   and consolidated Pharmacovigilance system including local health centers will allow to better

55   detect and report ADRs in order to provide knowledge to improve patient safety and

56   adherence of treatments.

57

58   2. METHODOLOGY OF INTERVENTION

59   2.1 Actors involved

60   The current project has been implemented by Barcelona Institute for Global Health (ISGlobal)

61   and Fundación Ciencia y Estudios Aplicados para el Desarrollo en Salud y Medio Ambiente

62   (CEADES). Both institutions shape the Bolivian Chagas Platform, a model to protocolize

63   together with the Chagas National and Departmental Program the attention for adults with *T.*

64   *cruzi* infection, and, by this way, to increase the number of adult patients diagnosed and

65   treated for CD [17]. The research was done in collaboration with the Pharmacovigilance Unit

66   (UNIMED) of the Bolivian Ministry of Health, the Pan American Health Organization (PAHO),

67   the Departmental Chagas Program of Cochabamba (ChDP) and the Tuberculosis Departmental

68   Program of Cochabamba (TBDP). A total of fourteen rural and urban primary and secondary

69   health care centers participated in the study, including four health care centers of the Bolivian

70   Chagas Platform.

71

72

2.2 Intervention plan

74   The intervention plan was performed in several steps:

A - Situational diagnosis

76   A situational diagnosis of Pharmacovigilance in the Department of Cochabamba was

77   performed in order to deeply study the causes of lack of reporting ADRs. The data collection

78   method was the use of a survey which included questions related with knowledge and attitude

79   towards Pharmacovigilance. All health professionals involved in CD treatment with at least one

80   year of experience working in the national health system were selected to participate. The

81   decision to include TB in the project was proposed by UNIMED after performing the situational

82   diagnosis.

83

B - Strategies to reinforce the current Bolivian Pharmacovigilance System

85   Strengthening the Bolivian Pharmacovigilance system was proposed in our project as a key

86   issue to reinforce therapeutic strategies in CD and TB. The Bolivian Pharmacovigilance system

87   is based on fill out the CRF elaborated by UNIMED by health care professionals. Then, the form

88   is sent to the healthcare network management, and finally it arrives to UNIMED. Together with

89   local health entities and UNIMED, the implementation of a new Local Case Report Form (CRF)

90   was suggested to the Bolivian Ministry of Health. The new form was elaborated based on the

91   follow-up form used in the Bolivian Chagas Platforms, the CRF established in the national

92   health system by UNIMED, and other CRFs used in other countries.

93

94   The CRF elaborated by UNIMED and the new CRF proposal were implemented in the Bolivian

95   Chagas Platforms located in the Department of Cochabamba (one in urban area and three in

96   rural areas), and in the primary and secondary national health care centers conforming the

97   network. The CRF provided by UNIMED was already established in some of the health care

98   facilities. Both forms were available in physical and electronic format, which was assigned

99   randomly in each health care center. To evaluate the intervention, a comparative analysis of

100   the use of the CRF established by UNIMED, the new CRF proposal, and the medical records to

101   report ADRs was performed. The medical records of the total patients starting treatment for

102   CD or TB were analyzed in order to detect how many of them suffered ADR during the

103   treatment.

104

105   A specific training on drug safety monitoring and ADR reporting was given, together with PAHO

106   and UNIMED, to all health professionals involved in CD and TB treatment. Three follow-up

107   visits were performed in each health care center.

108

109   **C - Analysis of the ADRs reported**

110   An analysis of the ADRs reported was performed, focusing on the following variables: total

111   patients reporting ADR; total patients abandoning treatment; affected organ-system; severity

112   of ADRs reported; recurrents ADRs; health care intervention; differences in reporting rates

113   between the CRF established by UNIMED, the new CRF proposal and the ADRS reported in the

114   medical records; differences in reporting rates between physical and electronic CRF format;

115   and differences in reporting rates between health care centers.

116

117   Patient abandonment was defined as the failure to complete medically indicated curative

118   therapy.

119

D - Data analysis

121 Absolute and relative frequency counts, and measures of central tendency (mean) were

122 calculated. GraphPad PRISM 5.0 software was used to draw graphs.

123

E - Ethics statement

125 The study protocol was approved by the Ethics Committee of the Hospital Clinic of Barcelona

126 and the Ethics Committee of CEADES.

3. RESULTS

3.1 Situational diagnosis: a challenging beginning

129 Health care professionals confirmed the importance of reporting ADRs, giving an average score

130 of 9,6 out of 10. This figure contrasts with the effectively reported ADR rate: 4,74 out of 10.

131

132 Causes for underreporting ADRs by health professionals were multifaceted. The most common

133 reason for not reporting ADRs was "lack of knowledge and awareness about

134 Pharmacovigilance and the duty of reporting" (50%). Health professionals also reported "lack

135 of availability of report forms" (18,75%), "forgetfulness to fill out the form" (12,5%), "forms

136 with too many variables" (6,25%), "patients forgetting to mention the ADR" (6,25%) and "ADRs

137 with no clinical significance" (6,25%). Results are summarized in Fig 1.

138

139 **Figure 1: Causes for underreporting of ADRs.**

140

141 From all the health care professionals participating in the survey, 53% reported ADRs using

142   patient's medical record, 27% using CRFs established by UNIMED, and 20% using CRFs

143   obtained from Bolivian ChDP. Regarding the CRF established by UNIMED, 62,5 % of health care

144   professionals were not aware of it. Of the 37,5% that were aware about the CRF from

145   UNIMED, only 33,3% of them were able to fill out the form correctly.

146

147   In terms of health care workers opinion, the most appropriate method to report ADRs was the

148   use of electronic CRFs (50%), the use of CRFs in physical format (31,25%) or irrelevant

149   (18,75%).

150

151   Regarding the issue of which ADRs should be reported to UNIMED, 43,75% of the health care

152   professionals participating in our study considered important to report all type of ADRs,

153   31,25% to report moderate and severe ADRs, and 25% to report only severe ADRs.

154   Lack of feedback from UNIMED to health care professionals could be another cause for

155   underreporting of ADRs. A huge percentage of health care professionals (81,25%) considered

156   that receiving feedback from UNIMED would increase the reporting rate of ADRs.

157

158   ## 3.2 Evaluation of the intervention

159   From the 396 patients starting treatment for CD, 140 (35,35% of them) suffered ADR according

160   to the information collected in the medical records. Out of the total ADRs collected in the

161   medical records, 25% of them were classified as moderate or severe types, and should have

162   been reported to the Bolivian Pharmacovigilance system. Only 51,43% of them were reported

163   to UNIMED.

164

165   Regarding TB treatment, 9,89% of the total patients suffered ADR. Out of the total ADRs

166   collected in the medical records, 44% of them were classified as moderate or severe types, and

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167   should have been reported to the Bolivian Pharmacovigilance system. From all the ADRs that

168   should have been reported, 75% of them were reported to UNIMED.

169

170   Results are summarized in Fig 2.

171

172   **Figure 2: Summary of the intervention results.**

173   ## 3.3 Analysis of the ADRs reported

174   From a total of 396 patients participating in the study and starting treatment for CD, 140

	Cercado network	Sacaba network	Punata network	Villatunari network	Total
Total patients starting treatment	198	47	59	92	396
Total patients reporting ADR	89 (50%)	22 (46,81%)	10 (16,95%)	19 (20,65%)	140 (35,35%)
Total patients abandoning treatment	24 (15,66%)	10 (21,28%)	5 (8,47%)	11 (11,96%)	50 (12,63%)

175   (35,35%) reported with ADRs. Patient abandonment was of 12,63%. Results are shown in table

176   1.

177

178   **Table 1: Total patients starting treatment, reporting ADRs, and abandoning treatment for CD**

179   **in the Bolivian Chagas Platforms located in the Department of Cochabamba and the primary**

180   **and secondary national health care centers included in the study.**

181

182   From 91 patients starting treatment for TB, 9 (9,89%) reported with ADRs, and the percentage

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183   of patient abandonment was 2,20%. Results are shown in table 2.

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189   **Table 2: Total patients starting treatment, reporting ADRs, and abandoning treatment for TB**

190   **in the primary and secondary national health care centers included in the study.**

	Cercado network	Sacaba network	Punata network	Villatunari network	Total
Total patients starting treatment	45	27	5	14	91
Total patients reporting ADR	7 (15,56%)	0 (0%)	1 (20%)	1 (7,14%)	9 (9,89%)
Total patients abandoning treatment	2 (4,44%)	0 (0%)	0 (0%)	0 (0%)	2 (2,20%)

191

192   Concerning CD, 35% of the total ADRs presented during treatment were dermatological, 29%

193   affected the central nervous system, 20% were gastrointestinal, and 16% affected other organs

194   or systems. Most of the ADRs presented during CD treatment were mild (74%), whereas 15%

195   were classified as mild/moderate, 10% as moderate, and 1% as severe. When focusing on the

196   health care intervention, nearly all ADRs were treated in the primary health care center (99%),

197   and only 1% had to be referred. Finally, the majority of the ADRs were non-recurrent (72%),

198   while 28% were recurrent ADRs.

199

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200   Regarding the characteristics of the ADRs presented during TB treatment, 36,36% of the total

201   ADRs presented were dermatological, 36,36% gastrointestinal, and 27,27% affected the central

202   nervous system. In terms of severity, 56% of the ADRs presented were classified as mild, 33%

203   were considered moderate, and 11% were severe. Regarding health care intervention, 56% of

204   the ADRs presented were treated in the primary health care center, 33% were referred, and

205   11% were not reported. Lastly, most of the ADRs presented were non-recurrent (78%), while

206   22% of them were recurrent.

207

208   4. DISCUSSION

209   Pharmacovigilance programme is an important component of National Healthcare Systems

210   (NHS). Data coming from Pharmacovigilance programme is essential to ensure safety and

211   effectiveness of drugs and to provide information concerning regulatory actions [18]. The

212   efforts of the Bolivian Ministry of Health to increase access to treatment for CD and TB require

213   strengthening the Pharmacovigilance system.

214

215   Despite having developed tools to report ADRs, Bolivian Pharmacovigilance System was not

216   well known for most health professionals up to now. Together with UNIMED, the ChDP and the

217   TBDP, an extended lack of knowledge and awareness about Pharmacovigilance was detected,

218   as well as the duty of reporting, and the lack of reporting ADR forms provided by UNIMED.

219   Insufficient training for healthcare professionals was the most important and urgent weakness

220   detected, especially concerning the primary national health care centers located in rural areas.

221   Training and follow-up on drug safety monitoring and ADR reporting was performed to all

222   health professionals involved in CD and TB treatment. A more specific training on

223   Pharmacovigilance was provided to all health professionals working in the national health care

224   centers of rural areas (departments of Villatunari and Punata).

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225

226   Although our project has shown interesting results, it is important to highlight that to reinforce

227   the Bolivian Pharmacovigilance System requires persistence and an active follow-up with

228   actors directly implicated in the NHS. This study emphasizes the importance of an educational

229   intervention to change attitude towards ADR reporting among healthcare professionals.

230   However, since it was a particular intervention, its long-term effect could not be measured.

231   Out of the total moderate and severe ADRs presented during CD treatment, only half of them

232   were reported to the Bolivian Pharmacovigilance system. Regarding TB, 25% of the moderate

233   and severe ADRs presented were not reported to the Bolivian Pharmacovigilance system. It is

234   important to notice that health care professionals are more used to report ADRs related to TB

235   than to CD, even though CD has been declared as a health priority for the Ministry of Health

236   [19]. TBDP had a pioneering role in promoting national ADR reporting system and providing

237   training for health care professionals [20]. Due to the characteristics of the current therapeutic

238   schemes and the scaling-up of Chagas treatment, ChDP should put more emphasis on

239   Pharmacovigilance activities to help physicians in their clinical practice.

240

241   The percentage of patient abandonment was 12,63% in CD patients, and 2,20% in TB patients.

242   It is highlighted that although abandonment levels may seem not to be high in TB, TB

243   treatment abandonment has fatal consequences for patients, which also become potential

244   sources of infection and resistance to available drugs [21].

245

246   Differences in reporting rates between the CRF established by UNIMED and the new CRF

247   proposal were not found. However, the new proposal of CRF results in better quality of data

248   collected. Information about the characteristics of presented ADRs in terms of severity,

249   affected organ-system, clinical suspicion of recurrence, and health care intervention is

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250   collected in the CRF proposal. Better designed, user-friendly and standardized reporting forms

251   would improve the process of capturing accurate information about ADR events [18]. New

252   tools adapted to the reality of health care workers are needed in order to strengthen the

253   current Bolivian ADR reporting system.

254

255

256   Lack of internet access is still an important problem in some regions of Bolivia, especially in

257   rural areas. In several rural and urban health care centers included in our study internet

258   connectivity was limited, and it was not possible to implement the CRF in electronic format.

259   Nevertheless, other possibilities could be explored in order to overcome this limitation. Apps

260   or electronic devices working in and offline mode could be an alternative [22]. Besides, some

261   of the health care facilities participating in the study are currently under renovation, and it was

262   considered important to have both forms (the CRF established by UNIMED and the new CRF

263   proposal) available in electronic format in order to facilitate reporting.

264

265   Lack of knowledge by health care professionals regarding the classification of ADRs by severity

266   was detected during the study. In several medical records, it was found the category «mild /

267   moderate», which is not correct. Lack of consensus on definition of ADR was also detected,

268   which is important also for the clinical management of the ADRs. In several medical records,

269   symptoms experimented by patients probably associated with concomitants pathologies

270   presented during CD or TB treatment were considered as ADRs. During our study, it was

271   considered as ADR every event classified as that in medical records. Nevertheless, there is a

272   need of overcoming these limitations.

273

274   Even if strengthen Bolivian Pharmacovigilance System has proven to be a good strategy to

275   improve patient health and increase adherence to CD and TB treatment, currently the system

276   still presents some weaknesses. According to all actors involved in our project, the

277   implementation of the next policies was suggested:

278

279   - To strengthen Pharmacovigilance activities in UNIMED, with external funding sources if it is

280   required, at least in a preliminary phase.

281   - To provide continued training in Pharmacovigilance for health care professionals, validated by

282   the Bolivian Ministry of Health and the Pan American Health Organization.

283

284   - To perform a continuous surveillance in Pharmacovigilance activities in health care centers

285   through monitoring and evaluation programs provided by UNIMED. In a preliminary stage, this

286   could require external technical support or funding sources.

287

288   - To integrate the topic Pharmacovigilance into the curricula in medical, pharmacy and nursing

289   schools, to provide excellent training to future health care professionals.

290

291   5. CONCLUSIONS

292   Overall, our findings suggest that Bolivian Pharmacovigilance system still presents some

293   challenges that should be addressed in the next years in order to achieve a strong, integrated

294   and consolidated ADR reporting system. The reinforcement of the Bolivian Pharmacovigilance

295   system is an ambitious project that should take a long-term perspective and several steps.

296   Continuity and perseverance are essential to achieve a solid and integrated reporting of ADR

297   system. UNIMED's current approach is to strengthen Bolivian Pharmacovigilance System in all

298   care levels, focusing on other neglected and prevalent pathologies in Bolivia and including all

299   the departments of the country. Several of our proposals are already in the process of being

300   implemented. However, the responsibility of leading these actions is still unclear. Further

301   projects are needed in order to achieve a strong and consolidated ADR reporting system to

302   improve patient safety, drug efficacy and adherence to treatment. A medium and long-term

303   follow up to evaluate their impact is also required.

304

305

306   6. ACKNOWLEDGEMENTS

309

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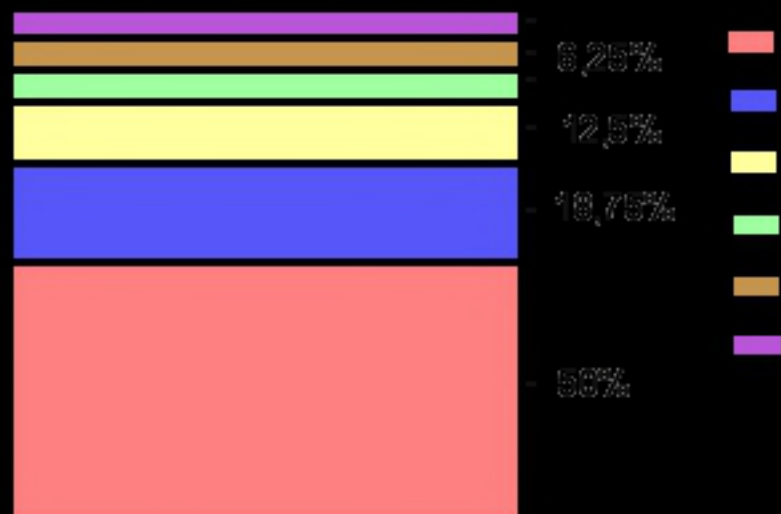370 2.

16

Causes for underreporting of ADRs

6.25%

12.5%

18.75%

58%

Figure 1: Causes for underreporting of ADRs

ADRs reported to UNIMED (51,43%)

Moderate or severe ADRs (25% of the total ADRs)

Patients reporting ADR (35,35%)

Total patients starting treatment for CD

18

35

140

396

ADRs reported to UNIMED (75%)

Moderate or severe ADRs (44% of the total ADRs)

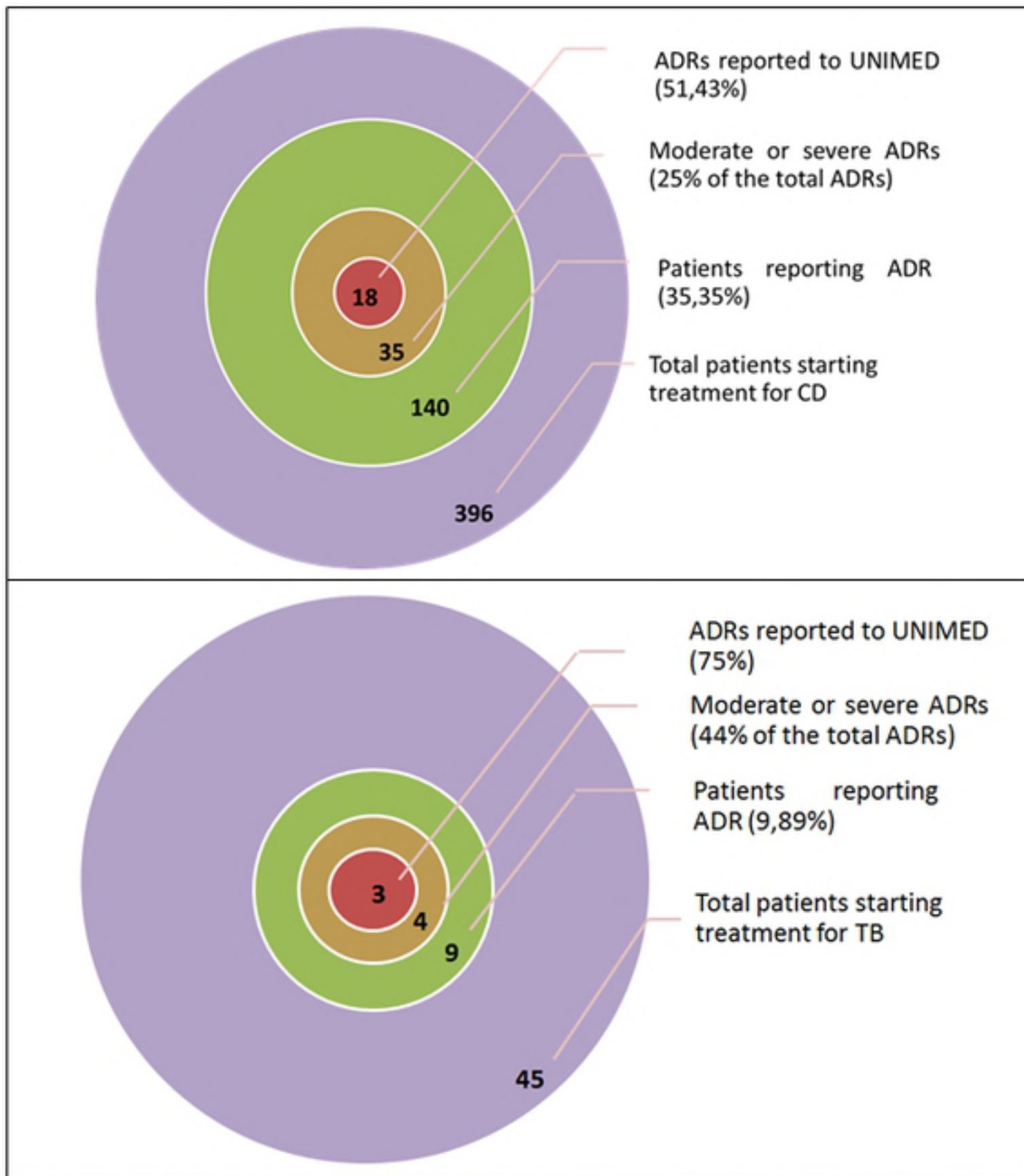Patients reporting ADR (9,89%)

Total patients starting treatment for TB

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Figure 2: Summary of the intervention results