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Adverse events associated with nifurtimox treatment for chagas disease in children and adults

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24 by drawing straws
25

26

27 **ABSTRACT**

28 **BACKGROUND:** Nifurtimox (NF) is one of the only two drugs currently available
29 for Chagas disease (ChD) treatment. However, there is scarce data on NF safety,
30 and many physicians defer or refuse NF treatment because of concerns about drug
31 tolerance.

32 **METHODS:** Retrospective study of adverse drug reactions (ADRs) associated with
33 NF treatment of ChD. Children received NF doses of 10-15 mg/kg/day for 60-90
34 days, and adults 8-10 mg/kg/day for 30 days.

35 **RESULTS:** 215 children (median age: 2.6yrs, range 0-17) and 105 adults (median
36 age: 34yrs, range 18-57) were enrolled. Overall, 127/320 (39.7%) patients
37 developed ADRs, with an incidence of 64/105 in adults, and 63/215 in children (OR
38 = 3.7, 95%CI [2.2;6.3]). We observed 215 ADRs, 131 in adults (median: 2
39 events/patient (IQR₂₅₋₇₅= 1-3) and 84 in children (median: 1 event/patient (IQR₂₅₋₇₅=
40 1-1.5) ($P_{\text{Adjusted}} < 0.001$). ADRs were mainly mild and moderate. Severe ADRs
41 were infrequent (1.2% in children and 0.9% in adults). Nutritional, central nervous
42 and digestive systems were the most frequently affected, without differences
43 between both groups.

44 Treatment was discontinued in 31/320 (9.7%) patients without differences between
45 groups. However, ADR-related discontinuations occurred more frequently in adults
46 than in children (OR = 5.5, 95%CI = [1.5;24]).

47 **CONCLUSIONS:** Our study supports the safety of NF for ChD treatment. Delaying
48 NF treatment due to safety concerns does not seem to be supported by the
49 evidence.

50

51 Background

52 Chagas disease (ChD) is a silent but devastating disease caused by infection with
53 the parasite *Trypanosoma cruzi*. The disease is endemic to the Americas, from the
54 USA to Argentina, with over 7 million people currently infected in Latin America.
55 ChD has expanded to many countries of the world via immigration, most cases
56 reported in Europe, North America, Australia and Japan(1).

57 Most patients are asymptomatic during acute ChD. The acute phase is followed by
58 a chronic asymptomatic stage that will eventually lead to irreversible heart disease
59 in up to 30% of the infected patients many years later(2). Over 7,000 deaths occur
60 yearly due to complications of Chagas.

61 The current treatment for ChD is limited to two nitro-heterocyclic drugs, nifurtimox
62 (NF) and benznidazole (BZ), both with similar effectiveness. Despite both drugs
63 having been available since the early 70s, treatment recommendations vary
64 significantly from country to country and the evidence-base for the current
65 treatment regimens is limited. This failure to treat may possibly be explained by
66 many obstacles, including health care providers' low awareness of the diseases
67 and its treatment options, overblown concerns about side effects, low access to
68 healthcare for many patients, lack of an optimal straightforward test of treatment
69 response, widespread drug shortages and irregular supplies, and regulatory
70 barriers .

71 The most commonly observed NF ADRs are anorexia and weight loss, irritability,
72 sleepiness, and other nervous system signs and symptoms (4, 5). NF is also
73 associated with rash, pruritus, and drug-associated hepatitis but less frequently
74 than BZN. Depression, peripheral neuropathy, and psychiatric symptoms have also
75 been reported. Similar to BZN, NF-associated ADRs seem much more common
76 and severe in adults (6)and are usually mild in children, including neonates (7, 8) .
77 However, current tolerability data comes mainly from small cohort studies. The
78 pharmacological basis for the differences in the incidence of adverse events
79 remain to be studied (9).

80 Here, we present results from a large cohort of ChD patients including infants,
81 children and adults treated with NF, describing and comparing safety among adults
82 and pediatric patients.

83 Results

84 Population characteristics

85 Medical records of ChD patients treated at our Institution were reviewed, and 372
86 patients who were prescribed NF were identified. However, 52 patients were
87 excluded because they did not start treatment (i.e. did not fill in NF prescription).
88 The remaining 320 patients were included in the study. A total of 215 pediatric
89 patients [0-17yrs) and 105 adults were included. Among children were: n=56 (0 -
90 7mos) n=43 (8mos - 1yr), n=44 (2 - 6yrs), n=37 (7 - 11yrs) and n=35 (12-17yrs). A
91 low rate of loss to follow-up was observed, as only 16/320 (5%) patients
92 abandoned the study (see flowchart diagram in Figure 1).

93 In general, male and female subjects were well balanced in children but not in
94 adults where 87.6% of subjects were female (most of them were mothers of
95 children assisted in our service). The route of infection was: congenital in 131,
96 undetermined in 154, vectorial in 32 and by blood transfusion in 3 cases (Table 1).

97 Overall, most patients were asymptomatic 289/320 (90.3%) and only 31/320
98 (9.7%) were symptomatic. Considering the route of infection, patients infected by
99 the vector route were predominantly symptomatic 12/32 (37.5%) and the most
100 frequent symptom was the ocular chagoma in 11/12 cases. In patients infected by
101 the remaining routes (congenital, undetermined and blood transfusion),
102 symptomatic cases were infrequent 19/288 (6.6%). Symptomatic cases were
103 observed mainly in infants under 2 years 16/19 (84.2%), and the most affected
104 organ was the liver (12/19 cases).

105 A clinical improvement was observed in all but one symptomatic patient during
106 treatment. Only one 3-month-old infant, coinfecting with *T.cruzi* and HIV by the
107 transplacental route, did not show clinical improvement. , The patient developed
108 encephalitis and myocarditis related to HIV infection, and died during NF treatment
109 due to respiratory complications.

110 ADRs incidence and relationship

111 Overall, 127/320 patients (39.7%) developed ADRs, with an incidence in adults of
112 64/105 (60.9%), and of 63/215 (29.3%) in children (OR = 3.7, CI95% = [2.2 - 6.3];
113 $P_{\text{Adjusted}} < 0.001$).

114 A total of 215 ADRs in 127 patients were observed. In 64 adults, 131 ADRs were
115 observed with a median of 2 events per patient (IQR₂₅₋₇₅ = 1-3) and in 63 children,

116 84 ADRs were observed with a median of 1 event per patient (IQR₂₅₋₇₅ = 1- 1.5);
117 ($P_{\text{Adjusted}} < 0.001$).
118 NF-related ADRs were more frequent in adults (79.7%) than in children (7.9%)
119 (OR=9.9, CI95% = [3.7 - 33]; $P_{\text{Adjusted}} < 0.001$; see Table 2 for further details). No
120 significant differences were observed in the amount of ADRs comparing patients
121 during the acute (vectorial and infants younger than 8 months of age) and the
122 chronic phase of infection ($P_{\text{Adjusted}} = 0.4$).
123 The number of ADRs was associated with incomplete treatment: 2.58
124 events/patient in subjects that discontinued treatment vs 1.55 events/patient in
125 those with completed treatment ($P_{\text{Adjusted}} < 0.001$). Moreover, differences remained
126 when considering both cohorts separately (adults: $P_{\text{Adjusted}} = 0.028$; children:
127 $P_{\text{Adjusted}} = 0.016$).
128 The profile of the 215 ADRs is shown in Table 3. The systems most commonly
129 affected were nutritional 75/215 (34.9%), Central Nervous System (CNS) 61/215
130 (28,4%) and digestive 38/215 (17.7%) without differences between adults and
131 children. Few adverse skin effects (20/215, 9.3%) were observed in both groups
132 and hematological ADRs (7/215 events) were observed only in children (OR = Inf,
133 CI95% = [2.3 - Inf]; $P_{\text{Adjusted}} = 0.005$).
134 Time of onset of ADRs was recorded for 130/215 ADRs in 64/127 patients (50.4%).
135 Overall, 93.8% of ADRs appeared within 30 days of treatment. ADRs median onset
136 time (IQR₂₅₋₇₅) was: 5 (2.5 - 10.2) days for digestive, 5.5 (1.5 - 11) days for CNS, 8
137 (0.75 - 26) days for nutritional, and 13 (10 - 20) days for skin.
138 ADRs had an earlier onset in adults, who presented a median onset time of 6.5
139 days (IQR₂₅₋₇₅ = 1.5 - 9), compared to children, who presented a median onset time
140 of 12 days (IQR₂₅₋₇₅ = 9.7 - 21; $P_{\text{Adjusted}} < 0.001$).

141 **Severity**

142 ADRs severity is described in Table 2. Most ADRs were mild (74.9%) and
143 moderate (16.3%) and resolved without sequelae. Severe ADRs were infrequent:
144 2/215 (0.9%). Severe ADRs occurred in 1 adult and in 1 child (see Table 2). The
145 adult was a woman in her 30's, who developed a headache with a defined
146 relationship to NF. ADR resolved without consequences, but NF treatment was
147 discontinued. The child was in the 8mos-2yrs age range, who presented severe
148 leukopenia, but also resolved without consequences and he was able to complete
149 treatment.
150 The severity of ADRs was associated with treatment discontinuation in adults, with
151 67% of discontinuations in the 15 subjects that presented moderate/severe ADRs
152 compared to 6.1% in the 49 subjects that presented mild ADRs (OR = 27.8, CI95%
153 = [5.1 - 212]; $P_{\text{Adjusted}} < 0.001$). In children no association was observed (OR = 2.4,
154 CI95% = [0.04 - 35]; $P_{\text{Adjusted}} = 0.4$).

155 Serious events were observed in 2 patients. One patient showed a serious event
156 unrelated to NF. The patient died due to complications related to HIV infection and
157 it was described previously. The other patient, a female in her 30's (not the one
158 mentioned in the previous paragraph), presented tremors, dysarthria and panic
159 attacks which required hospitalization. This patient made a full recovery, but
160 treatment was discontinued.

161 **Treatment completion**

162 Overall treatment was completed in 289/320 patients (90.3%) without differences
163 between children (92.6%) and adults (85.7%; Table 4). Treatment discontinuation
164 took place in 31/320 (9.7%) patients, but only 14/320 (4.4%) were related to ADRs
165 (Table 5). ADRs-related discontinuations occurred more frequently in adults (9.5%)
166 than in children (1.9%; OR = 5.5, CI95% = [1.5 - 24]; $P_{\text{Adjusted}} = 0.008$). Notably, the
167 main cause of treatment discontinuation in children was related to moderate skin
168 ADRs (3/4 children, see tables 4 and 5).

169 A total of 20/320 (6.2%) subjects temporarily interrupted NF (see table 4), without
170 differences among adults (9.5%) and children (4.7%, OR = 2.1, CI95% = [0.77 -
171 5.9]; $P_{\text{Adjusted}} = 0.14$). Temporary interruption causes were in 7 adults and 5
172 children due to ADRs and the remaining 8 patients by personal decision. The
173 median temporary interruption length was 7 days (IQR₂₅₋₇₅: 2- 9 days) with no
174 differences between adults and children.

175 ADRs leading to temporary treatment interruptions were digestive (5), CNS (3),
176 skin (2), cardiovascular (2), and nutritional (2) among adults, and digestive (2), skin
177 (2) and hematologic (2) among children. Treatment discontinuation occurred in 4 of
178 these 12 patients (2 adults, 2 children). The remaining patients completely
179 recovered after symptomatic treatment and/or transient interruption of NF.

180 For those 289 patients who completed treatment, mean dose, number of tablets
181 and the length of treatment are described in Table 6.

182 **Pediatric cohort analysis**

183 A sub-analysis by age group of the pediatric cohort was carried out to elucidate
184 whether there was any trend in the number, frequency or type of ADRs.

185 A high rate of treatment completion (92.6%) was observed without differences
186 within pediatric age groups (table 7).

187 No significant differences among pediatric subgroups were observed in the rates of
188 temporary interruption or in the rate of ADRs (25-38%). In addition, a high

189 compliance (greater than 70%) was observed in all groups and notably > 90%) in
190 patients under 2 years old (Table 7).

191 The most frequently observed pediatric ADRs were nutritional, followed by CNS
192 adverse reactions, without clear differences among age groups. Headache was
193 most frequent in children older than 7 years of age. Digestive and hematological
194 events were mainly observed in children younger than 2 years old (Table 8).

195 Discussion

196 We present a large retrospective study of ChD patients (children and adults),
197 treated with NF. We observed a low loss to follow-up, similar to other prospective
198 pediatric and adult ChD studies (7, 8, 10, 11). Our service followed the standard of
199 care guidelines for CD patients. However, as with any retrospective study
200 conducted over a long period of time, possible sources of bias must be considered,
201 due to insufficient detailed information about the incidence or severity of ADRs

202 ADRs incidence in our study was strongly associated with patient age, since adults
203 had higher incidence of ADRs and related treatment discontinuations than children.
204 Moreover, NF-related ADRs were significantly more frequent in adults. Although
205 pediatric pharmacologic studies on NF are still lacking, it is possible that observed
206 differences in incidence of ADRs among the pediatric and adult sub-populations
207 could be due to age-related differences in drug metabolism. NF is metabolized in
208 the liver, and, similar to many other drugs (12–14), it would be expected to
209 undergo faster liver clearance in children compared to adults, leading in shorter
210 half-lives and steady-state plasma concentrations. Pharmacological NF studies are
211 currently underway to clarify this issue (www.clinicaltrials.gov NCT01927224,
212 NCT02625974).

213 NF related ADRs had a lower incidence in our study compared to previous reports
214 in children (6, 8, 10) and in adults (4, 6, 11) Moreover, the rate of ADRs per patient
215 in our adult cohort was 4-fold lower than the reported in previous studies (11).
216 These differences could be explained by a larger sample size of our cohort that
217 would yield a more accurate estimate of the incidence of ADRs and a shorter time
218 of treatment (30 days) prescribed in our patients. However, some alternative
219 explanations are possible, such as socio-economic, ethnical differences among the
220 studied populations, detection bias (our data were retrospectively collected for this
221 analysis), or other yet unknown issues.

222 A high incidence of ADRs in patients with acute oral acute *T.cruzi* infection was
223 reported (6). In our study we did not observe a higher incidence of ADRs in

224 patients during the acute phase of infection. This difference could be related to the
225 different route of infection, mainly congenital, and that the majority of our cases
226 were asymptomatic or with mild symptoms of infection

227 Regarding severity, the ADRs observed in our cohort were mostly mild. Severe
228 events were infrequent. and all patients recovered with no sequelae. This is
229 comparable to previous studies in children (8, 10). However, in adult patients, we
230 report a lower incidence of severe and serious adverse events than previous
231 studies(4, 11).

232 ADRs appeared earlier in adults than in children but most of them occurred within
233 the first month of treatment, suggesting that most NF ADRs are not dependent on
234 cumulative doses.

235 ADRs profiles were similar between pediatric and adult populations, except for
236 hematological ADRs, which appeared only in children, mainly those under 2 years
237 of age. The most frequent ADRs were nutritional, mainly hyporexia and weight
238 loss, in line with the observations of many other ChD researchers (4, 7, 8, 11)

239 CNS ADRs are a major concern. Seizures and psychiatric ADRs related to NF
240 have been previously described (15). NF has a high level of fat solubility and is well
241 distributed throughout the tissues, including the CNS. Even though NF is a
242 substrate of breast cancer resistance protein (BCRP), which may be responsible
243 for the active transfer of NF out of the CNS, it is possible that some patients may
244 have BCRP polymorphisms that decrease this transfer, thus exposing them to high
245 level of NF in the CNS for longer periods of time (i.e. exposing them to CNS ADRs)
246 (16, 17). However, this remains a hypothesis to be tested. We observed mostly
247 headaches and CNS irritability as NF ADRs (16). An adult patient presented
248 tremors, dysarthria and panic attacks which required hospitalization, but recovered
249 without consequences after temporary treatment interruption. Evaluation of CNS
250 ADRs such as headaches, was difficult in children and particularly in infants
251 because only older children can accurately express these symptoms. However,
252 associated signs, such as unexplained irritability, food refusal, or vomiting, were
253 not reported by caregivers or observed by our pediatricians who have significant
254 experience in evaluating ChD pediatric patients.

255 The profile of digestive ADRs was similar to that reported in other NF studies (4, 5,
256 10, 11, 18). In children, digestive ADRs could be related to the lack of an
257 appropriate pediatric formulation of NF which requires pill fractioning. As pill
258 fragments are not easily (or willingly) swallowed by small children, this sometimes
259 results in vomiting and other problems that may not be specifically related to the
260 active drug. A new pediatric NF formulation in the late stages of clinical
261 development (clinicaltrials.gov NCT02625974), over time, would eventually be

262 helpful to address the pediatric formulation gap and possibly decrease the
263 incidence of digestive ADRs.

264 Skin reactions are the main ADRs observed during treatment with the alternative
265 drug BZ (19), but are much less frequently described with NF. Accordingly, we
266 observed few skin manifestations in our cohort, and only 3 children developed skin
267 reactions that led to treatment discontinuation. The differences in ADR profiles
268 between BZ and NF are not clearly explained to date, particularly given that they
269 are both nitro-drugs. Unfortunately, NF metabolism, and metabolite profiles for both
270 drugs remain poorly studied, which hampers any speculation on the
271 pharmacological reasons behind these ADR differences (20, 21).

272 Pediatric treatment discontinuation rates due to NF ADRs in our study were
273 comparable with those in other studies (8, 10). Even though we observed higher
274 discontinuation rates in adults compared to children, these adult rates (i.e. 14.3%)
275 were lower than those reported in previous studies, which ranged from 19.8% to
276 43.8% (4, 11). This difference could be due to the fact that most of the adult
277 patients in our study were relatives of previously treated and cured children, to
278 whom we offered treatment as part of our ChD family screening and treatment
279 protocol. This population is highly motivated to persist and complete treatment.

280 In summary, our results suggest that NF is a safe drug to use in both pediatric and
281 adult ChD patients. Considering the retrospective nature of the study, these results
282 are not conclusive and further prospective studies would be required in order to
283 confirm our results.

284 Since more primary infections of ChD occur during childhood, early diagnosis and
285 treatment of children is vital to prevent long-term ChD sequelae. In the light of our
286 findings, which strongly suggest, that NF is safe in childhood, we believe that
287 treatment should not be delayed.

288

289 **Methods**

290 **Study design and population**

291 This is a retrospective age-stratified study to assess safety and tolerability of oral
292 NF in subjects with ChD.S All patients were treated and followed-up at the
293 Parasitology and Chagas service, Hospital de Niños "Ricardo Gutiérrez", Buenos
294 Aires, Argentina from January 1980 to July 2019.

295 Patients were stratified according to age. Sub-analysis among children was done
296 considering the following age groups: (0 - 7mos), (8mos - 1yr), (2 - 6yrs), (7-
297 11yrs), (12 - 17yrs).

298 **Chagas Disease diagnostic criteria:** For infants younger than 8 months: direct
299 observation of *T.cruzi* using parasitological concentration method (microhematocrit
300 test, MH) or xenodiagnosis (XD); for older patients: 2 reactive serological tests:
301 Enzyme Linked Immunosorbent Assay (ELISA), Indirect Hemagglutination (IHA) or
302 Direct agglutination (DA).

303 Exclusion criteria: Cases where nifurtimox was prescribed but not taken (patients
304 did not come back; n = 52) or cases where medication data was not properly
305 documented. (n = 10).

306 Study population: For the safety analysis, all patients who started treatment were
307 considered, regardless of whether or not they completed the treatment.

308

309 **Treatment**

310 NF treatment (120-mg tablets, Bayer) was prescribed in doses of 10-15 mg per kg
311 per day divided in two or three daily doses for 60 to 90 days for infants and
312 children, and 8-10 mg per kg for 30 days for adults, according to national
313 guidelines at the moment of diagnosis. Note that regimens were modified for
314 shorter treatment in the last years. Enrollment of children started in January 1980,
315 and enrollment of adults started in July 2008. Infant NF doses were provided as
316 fractionated tablets prepared by a pharmacist and administered with water or
317 mother's milk. Medication was provided to patients or their guardians in monthly
318 batches, and compliance was assessed by counting remaining tablets at each visit.
319 Treatment was considered complete when patients took the medication for at least
320 60 days for children and 30 days for adults.

321 **Data Collection**

322 Data were collected from medical records of treated patients and entered into an
323 Access clinical database (ACD) designed for this study. All individual datasets
324 were anonymized.

325 Demographic data, clinical and biochemical assessments and complementary
326 studies were collected during follow-up. Baseline data values were obtained at the
327 beginning of the treatment. Following the standard of care of our service for CD
328 treated patients, visits were carried out at 7, 30 days and at the end of treatment,

329 every 3 months during the first-year post-treatment and every 6 -12 months
330 thereafter.

331

332 ADRs were evaluated through laboratory tests, clinical interviews and physical
333 examinations, and classified according to World Health Organization (WHO)
334 definitions (22, 23). Causality assessment was performed using the WHO criteria
335 for causality assessment

336 Information on treatment duration and dosage, temporary interruptions and
337 concomitant medications was systematically collected from medical records and
338 documented in the clinical Database.

339 **Statistical Analysis**

340 Continuous variables were expressed with mean and median, as applicable, with
341 the corresponding standard deviation or interquartile range. Categorical variables
342 were expressed in percentages. To test for significance, as appropriate, T test or
343 Wilcoxon unpaired rank test (W.T.) for continuous variables and Fisher exact tests
344 (F.E.T.) for categorical ones. P-values were adjusted by false discovery rate
345 (Benjamini-Hochberg procedure). Adjusted p-values with $P_{\text{Adjusted}} < 0.05$ were
346 considered statistically significant. The statistical package R was used (24).

347 **Ethics statement**

348 Study protocol was approved by the research & teaching committee and the
349 bioethics committee of the Buenos Aires Children's Hospital "Dr Ricardo
350 Gutierrez". The protocol was registered at ClinicalTrials.gov (NCT#04274101).

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354 Scientific and Technical Research Council of Argentina (CONICET).

355 **Potential conflicts of interest**

356 JA is a consultant of Bayer. All other authors report no potential conflicts.

357 **FIGURES**

358 Fig. 1. Study flowchart. Medical records included in this study are described in the figure.

359 TABLES

360

Table 1. Demographic data.

	Children (%)	Adults (%)	Total Patients (%)
Gender			
F	109 (50.7)	92 (87.6)	201 (62.8)
M	106 (49.3)	13 (12.4)	119 (37.2)
Age (months)			
Median [Q1, Q3]	31.0 [6.00, 108] mos.	34 [29, 38] yrs.	-
Mean (SD)	59.5 (63.1) mos.	34.5 (7.37) yrs.	-
Min-Max	1.00-215 mos.	19-57 yrs.	-
Route of Infection			
Vector	22 (10.2)	10 (9.5)	32 (10.0)
Congenital	120 (55.8)	11 (10.5%)	131 (40.9)
Blood transfusion	1 (0.5)	2 (1.9)	3 (0.9)
Undetermined	72 (33.5)	82 (78.1)	154 (48.1)
Clinical Examination at diagnosis			
Asymptomatic	185(86.0)	104(99.0)	289(90.3)
Symptomatic	30(14.0)	1(1.0)	31(9.7)
Total	215(67)	105(33)	320(100)

361 F: Female, M: Male

362 Table 2. Adverse events classified by severity and their relationship to treatment

	Children		Adults	
	Patients (%) n = 63	Number of ADRs (%) n = 84	Patients (%) n = 64	Number of ADRs (%) n = 131
Severity				
Mild	47 (74.6)	60 (71.4)	54 (84.4)	101 (77.1)
Moderate	8 (12.7)	8 (9.5)	14 (21.9)	27 (20.6)
Severe	1 (1.6)	1 (1.2)	1 (1.6)	1 (0.8)
No-Data	11 (17.5)	15 (17.9)	1 (1.6)	2 (1.5)
Relationship				
Not Related	5 (7.9)	10 (11.9)	2 (3.1)	2 (1.5)
Unlikely	1 (1.6)	1 (1.2)	1 (1.6)	1 (0.8)
Probable	47 (74.6)	53 (63.1)	20 (31.2)	31 (23.7)
Certain	5 (7.9)	5 (6)	51 (79.7)	95 (72.5)
No-Data	11 (17.5)	15 (17.9)	1 (1.6)	2 (1.5)
Total	63 (100.0)	84 (100.0)	64 (100.0)	131 (100.0)

363 Relationship classification was recorded according to OMS criteria. For each age group, two columns are
 364 shown. The first one, *Patients with ADRs*, shows the number of patients presenting at least one ADR and its
 365 corresponding percentage. The second column, *Number of ADRs*, depicted the observed number of ADRs and
 366 its corresponding percentage. Notice that patients could present more than one ADR belong to different
 367 categories (i.e Mild - Moderate).

368

369

370 Table 3. ADR occurrence and patient incidence by organ system.

	Children		Adults	
	Patients (%) n = 63	Number of ADRs (%) n = 84	Patients (%) n = 64	Number of ADRs (%) n = 131
Body as a whole	1 (1.6)	1 (1.2)	4 (6.2)	4 (3.1)
Fever	1 (1.6)	1 (1.2)	2 (3.1)	2 (1.5)
Asthenia	-	-	2 (3.1)	2 (1.5)
Cardiovascular	-	-	2 (3.1)	2 (1.5)
Syncope	-	-	1 (1.6)	1 (0.8)
Tachycardia	-	-	1 (1.6)	1 (0.8)
Digestive	11 (17.5)	12 (14.3)	21 (32.8)	26 (19.8)
Vomiting	8 (12.7)	8 (9.5)	4 (6.2)	4 (3.1)
Nausea	2 (3.2)	2 (2.4)	8 (12.5)	8 (6.1)
Dyspepsia	1 (1.6)	1 (1.2)	8 (12.5)	8 (6.1)
Abdominal pain	1 (1.6)	1 (1.2)	4 (6.2)	4 (3.1)
Others	-	-	2 (3.1)	2 (1.5)
Hematological	6 (9.5)	7 (8.3)	-	-
Eosinophilia	3 (4.8)	3 (3.6)	-	-
Leukopenia	3 (4.8)	3 (3.6)	-	-
Plaquetopenia	1 (1.6)	1 (1.2)	-	-
Nutritional	30 (47.6)	31 (36.9)	40 (62.5)	44 (33.6)

Weight loss	13 (20.6)	13 (15.5)	33 (51.6)	33 (25.2)
Hyporexia	18 (28.6)	18 (21.4)	11 (17.2)	11 (8.4)
Musculoskeletal	1 (1.6)	1 (1.2)	2 (3.1)	2 (1.5)
Myalgias	-	-	2 (3.1)	2 (1.5)
Chest pain	1 (1.6)	1 (1.2)	-	-
CNS	19 (30.2)	22 (26.2)	28 (43.8)	39 (29.8)
Headache	6 (9.5)	6 (7.1)	20 (31.2)	20 (15.3)
Irritability	15 (23.8)	15 (17.9)	7 (10.9)	7 (5.3)
Dizziness	-	-	5 (7.8)	5 (3.8)
Others	1 (1.6)	1 (1.2)	5 (7.8)	7 (5.3)
Respiratory	1 (1.6)	3 (3.6)	-	-
Acute bronchitis	1 (1.6)	1 (1.2)	-	-
Rhinorrhea	1 (1.6)	1 (1.2)	-	-
Influenza Syndrome	1 (1.6)	1 (1.2)	-	-
Skin	6 (9.5)	7 (8.3)	10 (15.6)	13 (9.9)
Rash	6 (9.5)	7 (8.3)	6 (9.4)	6 (4.6)
Urticaria	-	-	4 (6.2)	4 (3.1)
Others	-	-	3 (4.7)	3 (2.3)
Psychiatric	-	-	1 (1.6)	1 (0.8)
Depression	-	-	1 (1.6)	1 (0.8)
Total	63 (100.0)	84 (100.0)	64 (100.0)	131 (100.0)

372 Detailed description of the 215 ADRs occurring in the 127 patients segregated by organ system.
373 For each age group, two columns are shown. The first column, *Patients with ADRs*, shows the
374 number of patients presenting at least one ADR and its corresponding percentage. The second
375 column, *Number of ADRs*, depicted the observed number of ADRs and its corresponding
376 percentage. Low frequency symptoms were grouped into a general category, namely, “*others*”:
377 *digestive: (epigastralgia; pyrrhosis). CNS:(depression; nightmare; dysarthria; insomnia; loss of*
378 *memory; panic attacks; tinnitus). Skin: (facial edema; pruritus).*
379

380

381 Table 4. Treatment discontinuation and interruption.

	Children (%)	Adults (%)	Total Patients (%)
Complete treatment			
Yes	199 (92.6)	90 (85.7)	289 (90.3)
No	16 (7.4)	15 (14.3)	31 (9.7)
Discontinuation cause			
Patient Decision	6 (2.8)	1 (1.0)	7 (2.2)
Adverse Effect	4 (1.9)	10 (9.5)	14 (4.4)
Death	1 (0.5)	-	1 (0.3)
Lost of follow-up	5 (2.3)	4 (3.8)	9 (2.8)
Treatment Complete	199 (92.6)	90 (85.7)	289 (90.3)
Temporary Interruption			
Yes	10 (4.7)	10 (9.5%)	20 (6.2)
No	205 (95.3)	95 (90.5)	300 (93.8)
Total	215 (67.0)	105 (33.0)	320(100.0)

382 Detailed description of reasons of treatment discontinuation and interruption for all patients included
 383 in this study (n = 320 patients).
 384

385 Table 5. ADRs causing treatment discontinuation.

	Age range (yrs.)	Gender	Symptoms	Treatment Length (days)	Second Treatment
Pediatrics	0-1	F	Irritability	15	NF, Completed
	7-17	M	Rash	15	-
	7-17	F	Rash	27	-
	2-6	M	Abdominal pain, Rash, Fever, Eosinophilia	21	-
Adults	30-39	F	Headache, Irritability, Nausea	3	BZ, discontinued because of ADR
	40-49	F	Hiporexia	23	BZ, Completed
	50-59	F	Hiporexia	11	BZ, Completed
	30-39	F	Syncope, Dizziness, Headache, Dyspepsia, Nausea	12	BZ, Completed
	40-49	F	Headache, Abdominal pain	15	-
	20-29	F	Abdominal pain, Vomiting, Myalgias	11	-
	30-39	F	weight loss, Irritability, tremors, dysarthria, Panic attack	18	BZ, discontinued because of ADR
	20-29	F	Rash, Itching, Headache, Dyspepsia	12	BZ, Completed
	30-39	F	Headache. Dizziness	8	BZ, Completed
	30-39	F	Psychomotor agitation	10	BZ, discontinued because of ADR

386 Detailed ADR description for those patients who discontinued treatment due to ADRs. NF: nifurtimox, BZ:
387 benznidazole. All patients had a good response to symptomatic treatment.

388 Table 6: Treatment description.

	Children	Adults	Total Patients
Dose (mg/kg body weight)			
Median [Q1, Q3]	11.0 [10.0, 12.0]	9.00 [8.20, 9.70]	10.0 [9.19, 12.0]
Missing (%)	5 (2.5)	-	5 (1.7)
Number of doses			
Median [Q1, Q3]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]	2.00 [2.00, 3.00]
Missing (%)	6 (3.0)	-	6 (2.1)
Days of treatment			
Median [Q1, Q3]	62.0 [60.5, 73.0]	30.0 [29.0, 32.0]	61.0 [33.0, 69.0]
Concomitant medication			
Yes (%)	3 (1.5)	-	3 (1.0)
No (%)	196 (98.5)	90 (100)	286 (99.0)
Compliance			
Yes (%)	166 (83.4)	75 (83.3)	241 (83.4)
No (%)	33 (16.6)	15 (16.7)	48 (16.6)
Temporary Interruption			
Yes (%)	7 (3.5)	8 (8.9)	15 (5.2)
No (%)	192 (96.5)	82 (91.1)	274 (94.8)
Total	199 (92.6)	90 (100)	289 (90.3)

389 Treatment dosification, length and concomitant medication for all patients that completed NF treatment
 390 (n=289).

391

392 Table 7: Treatment details for the pediatric cohort.

	(0-7mos) Patients (%) n = 56	(8mos - 1yr) Patients (%) n = 43	(2 - 6yrs) Patients (%) n = 44	(7 - 11yrs) Patients (%) n = 37	(12 - 17yrs) Patients (%) n = 35	Total Patients (%) n = 215
Complete Treatment						
Yes	53 (94.6)	41 (95.3)	41 (93.2)	35 (94.6)	29 (82.9)	199 (92.6)
No	3 (5.4)	2 (4.7)	3 (6.8)	2 (5.4)	6 (17.1)	16 (7.4)
Treatment discontinuation						
Patient decision	-	1 (2.3)	2 (4.5)	1 (2.7)	2 (5.7)	6 (2.8)
Adverse event	-	1 (2.3)	1 (2.3)	0 (0)	2 (5.7)	4 (1.9)
Death	1 (1.8)	-	-	-	-	1 (0.5)
Loss of follow-up	2 (3.6)	-	-	1 (2.7)	2 (5.7)	5 (2.3)
Temporary Interruption						
Yes	2 (3.6)	1 (2.3)	2 (4.5)	1 (2.7)	4 (11.4)	10 (4.7)
No	54 (96.4)	42 (97.7)	42 (95.5)	36 (97.3)	31 (88.6)	205 (95.3)
Compliance						
Yes	48 (90.6)	37 (90.2)	29 (70.7)	27 (73.0)	25 (71.4)	166 (83.4)

No	5 (9.4)	4 (9.8)	12 (29.3)	12 (27.0)	10(28.6)	33 (16.6)
Adverse Events						
Yes	14 (25.0)	14 (32.6)	17 (38.6)	11 (29.7)	7 (20.0)	63 (29.3)
No	42 (75.0)	29 (67.4)	27 (61.4)	26 (70.3)	28 (80.0)	152 (70.7)
Number of Events per patient.						
Median [Q1, Q3]	1.0 [1.0, 1.00]	1.0 [1.0, 1.0]	1.0 [1.0, 2.0]	1.0 [1.00, 1.0]	2.0 [1.0, 2.0]	1.0 [1.0, 1.5]

393 Treatment completion, compliance, interruption and discontinuation causes for different age groups
394 in the pediatric cohort. Also, the number and rates of adverse events are shown

395

396 Table 8: ADR occurrence and patient incidence by organ system in the pediatric cohort.

	(0-7mos)		(7mos-1yr)		(2 – 6yrs)		(7-11yrs)		(12-17yrs)	
	Patients with ADRs (%) n = 14	Number of ADRs (%) n = 17	Patients with ADRs (%) n = 14	Number of ADRs (%) n = 16	Patients with ADRs (%) n=17	Number of ADRs (%) n = 24	Patients with ADRs (%) n = 11	Number of ADRs (%) n = 13	Patients with ADRs (%) n = 7	Number of ADRs (%) n = 14
Body as a whole	-	-	-	-	1 (5.9)	1 (4.2)	-	-	-	-
Fever	-	-	-	-	1 (5.9)	1 (4.2)	-	-	-	-
Digestive	4 (28.6)	4 (23.5)	2 (14.3)	2 (12.5)	2 (11.8)	2 (8.3)	-	-	3 (42.9)	4(28.6)
Vomiting	4 (28.6)	4 (23.5)	2 (14.3)	2 (12.5)	1 (5.9)	1 (4.2)	-	-	1 (14.3)	1(7.1)
Nausea	-	-	-	-	-	-	-	-	2 (28.6)	2(14.3)
Dyspepsia	-	-	-	-	-	-	-	-	1 (14.3)	1(7.1)
Abdominal pain	-	-	-	-	1 (5.9)	1 (4.2)	-	-	-	-
Hematological	2 (14.3)	2 (11.8)	2 (14.3)	3 (18.7)	1 (5.9)	1 (4.2)	1 (9.1)	1(7.7)	-	-
Eosinophilia	-	-	1 (7.1)	1 (6.2)	1 (5.9)	1 (4.2)	1 (9.1)	1(7.7)	-	-
Leukopenia	2 (14.3)	2(11.8)	1 (7.1)	1 (6.2)	-	-	-	-	-	-
Plaquetopenia	-	-	1 (7.1)	1 (6.2)	-	-	-	-	-	-
Nutritional	6 (42.9)	6 (35.3)	8 (57.1)	8 (50)	8 (47.1)	8 (33.3)	5 (45.5)	5(38.5)	3 (42.9)	4(28.6)

Weight loss	1 (7.1)	1 (5.9)	4 (28.6)	4 (25)	3 (17.6)	3 (12.5)	3 (27.3)	3(23.1)	2 (28.6)	2(14.3)
Hiporexia	5 (35.7)	5 (29.4)	4 (28.6)	4 (25)	5 (29.4)	5 (20.8)	2 (18.2)	2(15.4)	2 (28.6)	2(14.3)
Musculoskeletal	-	-	-	-	-	-	1 (14.3)	1(7.1)	-	-
Chest pain	-	-	-	-	-	-	1 (14.3)	1(7.1)	-	-
CNS	3 (21.4)	3 (17.6)	3 (21.4)	3 (18.7)	8 (47.1)	10 (41.7)	5 (45.5)	6(46.2)	-	-
Headache	-	-	-	-	2 (11.8)	2 (8.3)	4 (36.4)	4(30.8)	-	-
Irritability	3 (21.4)	3 (17.6)	3 (21.4)	3 (18.7)	7 (41.2)	7 (29.2)	2 (18.2)	2(15.4)	-	-
Nightmare	-	-	-	-	1 (5.9)	1 (4.2)	-	-	-	-
Respiratory	-	-	-	-	-	-	1 (14.3)	3(21.4)	-	-
Acute bronchitis	-	-	-	-	-	-	1 (5.6)	1 (3.7)	-	-
Rhinorrhea	-	-	-	-	-	-	1 (5.6)	1 (3.7)	-	-
Influenza Syndrome	-	-	-	-	-	-	1 (14.3)	1(7.1)	-	-
Skin	2 (14.3)	2 (11.8)	-	-	2 (11.8)	2 (8.3)	1 (9.1)	1(7.7)	1 (14.3)	2(14.3)
Rash	2 (14.3)	2 (11.8)	-	-	2 (11.8)	2 (8.3)	1 (9.1)	1(7.7)	1 (14.3)	2(14.3)
Total	14(100)	17 (100)	14(100)	16(100)	17(100)	24(100)	11(100)	13 (100)	7 (100)	14 (100)

397

398 Detailed description of the 84 ADRs occurring in the 64 pediatric patients segregated by organ
 399 system. For each age group, the first column, *Patients with ADRs*, displays the number of patients
 400 presenting at least one ADR and its corresponding percentage. The second column, *Number of*
 401 *ADRs*, depicted the observed number of ADRs and its corresponding percentage.

402

403 **Bibliography**

- 404 1. Schmunis GA, Yadon ZE. 2010. Chagas disease: a Latin American health problem
405 becoming a world health problem. *Acta Trop* 115:14–21.
- 406 2. Altcheh JM, Freilij H. 2019. *Chagas Disease: A Clinical Approach*. Springer Nature.
- 407 3. Pereiro AC. 2019. Guidelines for the diagnosis and treatment of Chagas disease.
408 *Lancet* 393:1486–1487.
- 409 4. Jackson Y, Alirol E, Getaz L, Wolff H, Combescure C, Chappuis F. 2010. Tolerance
410 and safety of nifurtimox in patients with chronic chagas disease. *Clin Infect Dis*
411 51:e69–75.
- 412 5. Olivera MJ, Cucunubá ZM, Álvarez CA, Nicholls RS. 2015. Safety Profile of Nifurtimox
413 and Treatment Interruption for Chronic Chagas Disease in Colombian Adults. *The*
414 *American Journal of Tropical Medicine and Hygiene*.
- 415 6. Alarcón de Noya B, Ruiz-Guevara R, Noya O, Castro J, Ossenkopp J, Díaz-Bello Z,
416 Colmenares C, Suárez JA, Noya-Alarcón O, Naranjo L, Gutiérrez H, Quinci G, Torres
417 J. 2017. Long-term comparative pharmacovigilance of orally transmitted Chagas
418 disease: first report. *Expert Rev Anti Infect Ther* 15:319–325.
- 419 7. Freilij H, Altcheh J. 1995. Congenital Chagas' Disease: Diagnostic and Clinical
420 Aspects. *Clinical Infectious Diseases*.
- 421 8. Moya PR, Paolasso RD, Blanco S, Lapasset M, Sanmartino C, Basso B, Moretti E,
422 Cura D. 1985. [Treatment of Chagas' disease with nifurtimox during the first months of
423 life]. *Medicina* 45:553–558.

- 424 9. Garcia-Bournissen F, Altcheh J, Giglio N, Mastrantonio G, Della Védova CO, Koren
425 G. 2009. Pediatric Clinical Pharmacology Studies in Chagas Disease. *Pediatric Drugs*.
- 426 10. Bianchi F, Cucunubá Z, Guhl F, González NL, Freilij H, Nicholls RS, Ramírez JD,
427 Montilla M, Flórez AC, Rosas F, Saavedra V, Silva N. 2015. Follow-up of an
428 Asymptomatic Chagas Disease Population of Children after Treatment with Nifurtimox
429 (Lampit) in a Sylvatic Endemic Transmission Area of Colombia. *PLOS Neglected
430 Tropical Diseases*.
- 431 11. Forsyth CJ, Hernandez S, Olmedo W, Abuhamidah A, Traina MI, Sanchez DR,
432 Soverow J, Meymandi SK. 2016. Safety Profile of Nifurtimox for Treatment of Chagas
433 Disease in the United States. *Clin Infect Dis* 63:1056–1062.
- 434 12. Hines RN. 2007. Ontogeny of human hepatic cytochromes P450. *Journal of
435 Biochemical and Molecular Toxicology*.
- 436 13. Hines RN. 2008. The ontogeny of drug metabolism enzymes and implications for
437 adverse drug events. *Pharmacology & Therapeutics*.
- 438 14. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Steven Leeder J, Kauffman
439 RE. 2003. Developmental Pharmacology — Drug Disposition, Action, and Therapy in
440 Infants and Children. *New England Journal of Medicine*.
- 441 15. Wegner DH, Rohwedder RW. 1972. The effect of nifurtimox in acute Chagas'
442 infection. *Arzneimittelforschung* 22:1624–1635.
- 443 16. Watson CP, Dogruel M, Mihoreanu L, Begley DJ, Weksler BB, Couraud PO, Romero
444 IA, Thomas SA. 2012. The transport of nifurtimox, an anti-trypanosomal drug, in an
445 vitro model of the human blood–brain barrier: Evidence for involvement of breast
446 cancer resistance protein. *Brain Research*.

- 447 17. Garcia-Bournissen F, Altcheh J, Panchaud A, Ito S. 2010. Is use of nifurtimox for the
448 treatment of Chagas disease compatible with breast feeding? A population
449 pharmacokinetics analysis. *Arch Dis Child* 95:224–228.
- 450 18. Valencia NC, Mancilla M, Ramos D, Zulantay I, Molina M, Torres A, Corral G, Apt W.
451 2012. Tratamiento de la enfermedad de Chagas crónica en Chile: efectos adversos
452 de nifurtimox. *Revista Ibero-latinoamericana de parasitología* 71:97–108.
- 453 19. Altcheh J, Moscatelli G, Moroni S, Garcia-Bournissen F, Freilij H. 2011. Adverse
454 events after the use of benznidazole in infants and children with Chagas disease.
455 *Pediatrics* 127:e212–8.
- 456 20. Hall BS, Bot C, Wilkinson SR. 2011. Nifurtimox activation by trypanosomal type I
457 nitroreductases generates cytotoxic nitrile metabolites. *J Biol Chem* 286:13088–
458 13095.
- 459 21. Hall BS, Wilkinson SR. 2012. Activation of benznidazole by trypanosomal type I
460 nitroreductases results in glyoxal formation. *Antimicrob Agents Chemother* 56:115–
461 123.
- 462 22. Edwards IR, Ralph Edwards I, Aronson JK. 2000. Adverse drug reactions: definitions,
463 diagnosis, and management. *The Lancet*.
- 464 23. Edwards IR, Ralph Edwards I, Biriell C. 1994. Harmonisation in Pharmacovigilance.
465 *Drug Safety*.
- 466
- 467 24. R Core Team (2019). R: A language and environment for statistical computing. R
468 Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.

