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1 **A biological pharmacology network to secure the risk of drug-drug interaction with**  
2 **nirmatrelvir/ritonavir**

3 Florian Lemaitre<sup>1,2,3</sup>, Lidvine Boland<sup>4,5</sup>, Camille Tron<sup>1,2,3</sup>, Matthieu Grégoire<sup>6,7</sup>, Véronique Lelong-  
4 Boulouard<sup>8,9</sup>, Peggy Gandia<sup>10,11</sup>, Françoise Goirand<sup>12,13</sup>, Nicolas Gambier<sup>14</sup>, Christelle Boglione-  
5 Kerrien<sup>1,2,3</sup>, Bénédicte Franck<sup>1,2,3</sup>, Sébastien Lalanne<sup>1,2,3</sup>, Arnaud Devresse<sup>15,16</sup>, Sebastien Briol<sup>15,16,17</sup>,  
6 Vincent Haufroid<sup>4,5</sup> and Marie-Clémence Verdier<sup>1,2,3</sup> on behalf of the SFPT Therapeutic Drug Monitoring  
7 and Treatment Personalization group (STP-PT) of the French Society of Pharmacology and Therapeutics  
8 (SFPT)

9 <sup>1</sup> Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et  
10 travail) – UMR S 1085, F-35000 Rennes, France.

11 <sup>2</sup> INSERM, Clinical Investigation Center 1414, Rennes, France

12 <sup>3</sup> FHU SUPORT, Rennes, F-35000, France.

13 <sup>4</sup> Department of Clinical Chemistry, Cliniques universitaires Saint-Luc, Brussels, Belgium.

14 <sup>5</sup> Louvain centre for Toxicology and Applied Pharmacology (LTAP), Institut de Recherche Expérimentale  
15 et Clinique, Université catholique de Louvain, Brussels, Belgium.

16 <sup>6</sup> Nantes Université, CHU Nantes, Cibles et médicaments des infections et de l'immunité, IICiMed, UR  
17 1155, F-44000 Nantes, France.

18 <sup>7</sup> Nantes Université, CHU Nantes, Service de Pharmacologie Clinique, 9 quai Moncoussu 44093, F-  
19 44000 Nantes, France.

20 <sup>8</sup> Normandie Univ, UNICAEN, INSERM COMETE, U1075, Caen, F-14000, France.

21 <sup>9</sup> CHU de Caen, Pharmacology Department, Caen, F-14000, France.

22 <sup>10</sup> Laboratoire de Pharmacocinétique et Toxicologie, Institut Fédératif de Biologie, CHU de Toulouse,  
23 Toulouse, France.

24 <sup>11</sup> INTHERES, Université de Toulouse, INRAE, ENVT, Toulouse, France.

25 <sup>12</sup> Laboratoire de Pharmacologie et Toxicologie, Centre Hospitalier Universitaire Dijon-Bourgogne,  
26 Dijon, France

27 <sup>13</sup> University of Burgundy, Faculty of Medicine and Pharmacy, Dijon, France.

28 <sup>14</sup> CHRU-Nancy, Service de Pharmacologie Clinique et Toxicologie, F-54000 Nancy, France; Université  
29 de Lorraine, CNRS, IMoPA, F-54000 Nancy, France.

30 <sup>15</sup> Department of Nephrology. Cliniques universitaires Saint-Luc, Brussels, Belgium.

31 <sup>16</sup> Department of Surgery and Abdominal Transplant, Cliniques universitaires Saint-Luc, Brussels,  
32 Belgium.

33 <sup>17</sup> Department of Internal Medicine and Infectious Disease. Cliniques universitaires Saint-Luc, Brussels,  
34 Belgium.

35 **Corresponding author:** Florian Lemaitre, Department of Biological Pharmacology, Hôpital  
36 Pontchaillou, CHU de Rennes, 2, rue Henri Le Guilloux, 35000 Rennes, France

37 Mail : [florian.lemaitre@chu-rennes.fr](mailto:florian.lemaitre@chu-rennes.fr); Tel : +33 2 23 23 47 13 : Fax : +33 2 99 28 43 81

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41

42 **Abstract:**

43 Nirmatrelvir/ritonavir is a protease inhibitor antiviral drug indicated in the treatment of severe acute  
44 respiratory syndrome coronavirus-2 infections in high-risk patients for a severe disease. Unfortunately,  
45 ritonavir, used to boost nirmatrelvir pharmacokinetics, can also inhibit or induce the metabolism of  
46 other co-administered drugs substrates. This may lead to a subsequent risk of adverse drug reaction  
47 and lack of efficacy. In this study, we aimed at describing the expert advices provided by the biological  
48 pharmacology network of the SFPT (i.e. the therapeutic drug monitoring specialists working in the  
49 laboratories of the pharmacology departments in France/Belgium).

50 From February to August 2022, we collected all specialized advices provided by the biological  
51 pharmacology network of the SFPT. Seven pharmacology departments actively participated in the  
52 study (Brussels Saint-Luc Hospital in Belgium, Caen, Dijon, Nantes, Nancy, Rennes and Toulouse in  
53 France). We collected the following data: patient's age, date of nirmatrelvir/ritonavir initiation, clinical  
54 department requiring the expert advice, patient's treatments, and advice provided.

55 One hundred and six expert advice on 753 drugs were provided during the seven months of data  
56 collection. Two centers provided 83% of all the expert advice (around 8/month). Patients originated  
57 from a transplantation department in 65% of the cases. The most common request were for cardiac  
58 drugs (28%), immunosuppressive drugs (24%) and endocrine drugs (18%). The advice were distributed  
59 as follows: treatment continuation, treatment discontinuation during the antiviral course, dosage  
60 adjustment, and treatment switch in 59%, 28%, 11%, and 1.6% of the cases, respectively. Only 2 pieces  
61 of advice (0.3%) constituted treatment contra-indications. Drug monitoring was proposed in 10% of  
62 prescription lines.

63 Expert advice provided by the biological pharmacology network of the SFPT allows securing the  
64 combination of nirmatrelvir/ritonavir with other concomitant drugs. Most of eligible patients to the  
65 antiviral drug can benefit from it despite the risk of drug-drug interaction.

66

67 **Keywords:** COVID-19; Drug monitoring; Safety; Cytochrome P450; Antivirals

68

69 **Introduction:**

70 Nirmatrelvir/ritonavir (Paxlovid®) is a protease inhibitor antiviral drug indicated in the treatment of  
71 severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections in high-risk patients for a  
72 severe disease. The drug was shown to decrease the risk of hospitalization and death by 87% (1),  
73 making it a first line therapy with other options such as sotrovimab, remdesivir and bebtelovimab.  
74 Unfortunately, with the arisen of SARS-CoV-2 omicron subvariants, sotrovimab lost its activity (2).  
75 Regarding bebtelovimab, the drug has no phase III clinical trial data and remdesivir is an intravenous  
76 drug (3). Hence, apart from molnupiravir, which is not available in France, nirmatrelvir/ritonavir is the  
77 only orally administrated drug with such a high level of efficacy in preventing high-risk patients from  
78 progressing toward severe disease. It makes the drug appropriate for outpatient treatment, which also  
79 provides a key advantage in the prevention of communicable disease transmission. However, the  
80 antiviral drug also exposed patients to a particular risk of drug-drug interaction. Indeed, nirmatrelvir,  
81 the active antiviral component of the combination, is associated with ritonavir. Ritonavir is a well-  
82 known cytochrome P450 (CYP) 3A inhibitor and has been successfully combined with other protease  
83 inhibitors in the field of human immunodeficiency virus or hepatitis C virus infections. By inhibiting the  
84 CYP3A4 metabolism of nirmatrelvir and thus, decreasing its elimination, it allows maintaining high  
85 exposure of the antiviral drug, making it suitable for a twice-daily intake. Unfortunately, ritonavir can  
86 also inhibit the metabolism of other co-administered drugs substrates of CYP3A4. This may lead to the  
87 accumulation of these drugs in patients' organism with a subsequent risk of adverse drug reactions.

88 Besides its inhibitory effect on the CYP3A4 pathway, ritonavir also inhibits other CYP such as CYP2D6  
89 and membrane transporters such as P-glycoprotein (P-gp). On the opposite, ritonavir has an inducer  
90 effect on CYP1A2, CYP2C9, CYP2C19 and some UDP-glucuronyl transferase, catalyzing the enzymatic  
91 phase II metabolism of numerous drugs (4,5). It is noteworthy that the eligible population to  
92 nirmatrelvir/ritonavir is often polymedicated because of age and chronic disease burden.

93 These complex interactions with drug metabolism and transport make nirmatrelvir/ritonavir  
94 challenging to prescribe and require important knowledge and skills in drug-drug interactions to secure  
95 its use. That is why the French learning society of pharmacology (Société Française de Pharmacologie  
96 et de Thérapeutique (SFPT)) has issued a recommendation document to guide clinicians in prescribing  
97 nirmatrelvir/ritonavir to their patients (6). However, some complex situations require an individualized  
98 approach because of patient's disease history, multiple drug interactions, the need for treatment  
99 monitoring or other specific considerations. The SFPT has also built a framework aimed at providing  
100 expert advice on drug-drug interactions (DDI) to help clinicians in prescribing the drug. In this study,  
101 we aimed at describing the expert advice provided by the biological pharmacology network of the SFPT  
102 (i.e the therapeutic drug monitoring specialists working in the laboratories in the pharmacology  
103 departments in France or Belgium).

104

#### 105 **Methods:**

106 From February the 3<sup>rd</sup> 2022, the day of availability of nirmatrelvir/ritonavir in France, to August the  
107 31<sup>st</sup> 2022, we collected all specialized advice provided by the biological pharmacology network of the  
108 SFPT to medical doctors or pharmacists. Seven pharmacology departments actively participated in the  
109 study (Brussels Saint-Luc University Hospital in Belgium, Caen University Hospital, Dijon University  
110 Hospital, Nantes University Hospital, Nancy University Hospital, Rennes University Hospital and  
111 Toulouse University Hospital in France). The SFPT made available a list of contacts for clinicians to  
112 request experts and Experts have been contacted by phone calls or emails. We collected the following

113 data: patient's age, date of nirmatrelvir/ritonavir initiation, clinical department requiring the expert  
114 advice, patient's treatments, provided advice (treatment continuation without change, dosage  
115 adjustment and the magnitude of this adjustment, treatment discontinuation during antiviral co-  
116 administration, drug monitoring or contra-indication). As the data collection was anonymized, no  
117 demographic data outside of age and biological parameters were collected. The nature of the potential  
118 drug monitoring and the moment of proposed restart of the treatment have also been gathered. Data  
119 were then presented as median and interquartile range (IQR) for quantitative variables and as  
120 percentage for categorical variables.

121 The study received the Rennes University Hospital local ethics committee approval (N°23.16).

122

### 123 **Results:**

124 One hundred and six expert advice for one hundred and six patients regarding 753 prescribed drug  
125 lines of prescriptions were provided during the seven months of the study. It should be noted that the  
126 same drug prescribed in two different patients was considered as two prescribed drug lines. Two  
127 centers (Rennes University Hospital and Brussels Saint-Luc University Hospital) contributed for 83% (88  
128 pieces of advice) of all the expert advice provided. For these two centers, this represents 6.9 pieces of  
129 advice per month for the Rennes University Hospital (48 advices provided during 7 months) and 8.0  
130 pieces of advice per months for Brussels Saint-Luc Hospital (40 advices provided during 5 months as  
131 nirmatrelvir/ritonavir has been available a little bit later, in April 2022, in Belgium). Median [IQR] age  
132 of patients benefiting from an expert advice was 65[56-72] years. Most of the expert advice was  
133 requested from solid organ transplantation departments (69 patients, 65.1%) following by general  
134 practitioners (19 patients, 17.9%) and oncology departments (9 patients, 8.5%). Among the type of  
135 drugs for which an expert advice was requested, cardiac drugs were the most common drugs (28.2%  
136 of all prescribed drug lines, mainly antihypertensive and lipid-lowering drugs) followed by  
137 immunosuppressive drugs (24.0% of all prescribed drug lines) and endocrinology drugs (18.5% of all

138 prescribed drug lines) (Figure 1). Table 1 shows the details of the 30 most commonly requested drugs  
139 with tacrolimus, mycophenolic acid and acetyl salicylic acid being the 3 most frequently asked.  
140 Regarding the type of expert advice provided, most of the drugs prescribed (59.1%) could be  
141 maintained without any change in dosage, administration route or frequency. A temporary  
142 discontinuation of drugs during the antiviral treatment and up to a few days after the end of  
143 nirmatrelvir/ritonavir treatment has been proposed in 27.9% of all prescribed drug lines including  
144 statins, tacrolimus, mycophenolic acid... Atorvastatin was the statin with the highest request (n=23)  
145 followed by rosuvastatin (n=6), pravastatin (n=4), simvastatin (n=3) and fluvastatin (n=2).

146 A dosage modification, mainly to prevent overexposure of the drug associated with  
147 nirmatrelvir/ritonavir, has been proposed in more than one case out of 10 (11.1%), while a switch to  
148 another similar drug has been proposed in 1.6% of all prescribed drugs. Most of the proposed switch  
149 affected anticoagulants such as apixaban (n=6) or rivaroxaban (n=2). A clinical or biological monitoring  
150 was advised in 15.3% of all prescribed drug lines with 64% of these monitoring advices being a  
151 therapeutic drug monitoring, overwhelmingly for immunosuppressive drugs. Finally,  
152 nirmatrelvir/ritonavir has been denied in only 2 cases (1.9% of patients and 0.3% of all prescribed drug  
153 lines). In one case, it was a contra-indication to paclitaxel and in the other a contra-indication to  
154 amiodarone. The overview of the type of expert advice provided is summarized in Figure 2.

155

## 156 **Discussion:**

157 This study reports an original framework for expert pharmacological advices provided by therapeutic  
158 drug monitoring pharmacologist specialists working in the laboratories of the French and Belgian  
159 pharmacology departments. After nirmatrelvir/ritonavir drug approval, prescription has been reported  
160 to be challenging due to the DDI risk perception by clinicians. Indeed, some adverse events associated  
161 with the drug use have been reported with some of them being lethal (7). Nirmatrelvir/ritonavir  
162 prescription requires skills in DDI analysis and management, and planning dosage adjustment and

163 therapeutic monitoring can be really difficult for non-pharmacologist specialists, notably for drugs with  
164 a narrow therapeutic index (8,9). Although guidelines have been proposed to help clinicians dealing  
165 with this issue, the multidisciplinary approach including a specialist in pharmacology remains key to  
166 individualize the treatment, as recommended in Paxlovid SmPc (6,10). For years, pharmacologists  
167 specialized in therapeutic drug monitoring (TDM) have been involved in mitigating the DDI risk with  
168 ritonavir in particular in the setting of ritonavir-boosted treatment for HIV or HCV (11,12). This  
169 expertise has been used to implement a biological pharmacology network to secure the risk of drug-  
170 drug interaction with nirmatrelvir/ritonavir, whom results were reported in the present study. During  
171 the first weeks after drug approval, TDM specialists of the French and Belgian pharmacology  
172 departments offered expert advice aiming at: evaluating the possibility of combining  
173 nirmatrelvir/ritonavir with the treatments usually prescribed to a candidate-patient for an antiviral  
174 therapy, proposing treatment modifications and finally providing guidance on treatment monitoring.  
175 The results of this study indicate that nirmatrelvir/ritonavir prescription is possible whatever the  
176 therapeutic status of patients in almost every situation. Indeed, treatment was denied in less than two  
177 percents of patients (2 cases out of 106). Moreover, one of the two situations motivating a contra-  
178 indication of nirmatrelvir/ritonavir prescription was a combination between nirmatrelvir/ritonavir and  
179 amiodarone, which has been shown to be feasible upon amiodarone discontinuation during the  
180 antiviral treatment (13). As the antiviral treatment duration was a short 5-day course, it is probably  
181 possible to safely discontinue high-risk drugs for DDI, such as statins, without harming patients.  
182 However, some authors claims that statins treatment should not be discontinued and that it is possible  
183 to treat patients with statins poorly metabolized by CYP3A such as pravastatin and fluvastatin and even  
184 that the combination might be possible at the lowest dose with rosuvastatin and atorvastatin (14). This  
185 is, at least partially, contradicted by statins DDI study with antivirals boosted with ritonavir. For  
186 example, a short course ritonavir increases single dose atorvastatin AUC by a factor of 4.8 (15). And if  
187 the effect on rosuvastatin in the same study is modest (with a 1.9 increase in Cmax but a similar AUC),  
188 other data shows a mean AUC increase factor of 2.6 when rosuvastatin is combined with ritonavir-



189 boosted HVC antivirals (16). If fluvastatin interaction with ritonavir is largely undocumented,  
190 pravastatin pharmacokinetics relates to organic anion transporter polypeptide 1B1 and its AUC with  
191 ritonavir can range from +21% to +96% according to *SLCO1B1* genotype, which makes the interaction  
192 amplitude largely unpredictable (17).

193 Several requests for expert advice have also been made for immunosuppressive drugs. This is not  
194 surprising as these drugs present a narrow therapeutic index and because drug exposure variation can  
195 lead to severe adverse drug reactions. Treatment algorithms have been developed to adjust  
196 immunosuppressive drugs dosage during their combination with nirmatrelvir/ritonavir (18,19). The  
197 pharmacologists' expert advice allow planning a drug monitoring to ensure that dosage adjustments  
198 reached their desirable objectives. This can be a clinical monitoring (e.g arterial tension monitoring for  
199 antihypertensive drugs such as bisoprolol) or a biological monitoring. Again, therapeutic drug  
200 monitoring of immunosuppressive drugs is in the forefront in this study as it represents more than 2  
201 monitoring advice out of 3 provided by the pharmacologists. While still available in a limited number  
202 of centers, at-home monitoring of immunosuppressive drugs has also been proposed as a convenient  
203 alternative to standard therapeutic drug monitoring. It ensures preventing patients from being in close  
204 contact with other at-risk patients for severe disease and allows, for example in the case of tacrolimus,  
205 multiple sampling for the evaluation of drug exposure and for resuming immunosuppressive treatment  
206 at the end of the nirmatrelvir/ritonavir (9). As accumulation of tacrolimus has been described at the  
207 time of restarting tacrolimus, this is of utmost importance. On the other side, a limited number of  
208 advices have been given regarding oncology drugs (2.1%) and to a lesser extend regarding  
209 neuropsychiatric drugs (7.8%). This might appear unexpected given the fact that patients treated for a  
210 cancer were a subpopulation of particular interest for nirmatrelvir/ritonavir prescription as they  
211 belong to the high-risk population for severe COVID-19. The neuropsychiatric drugs also appears as a  
212 field of interest given the difficult therapeutic balance in this population, the frequent prescription of  
213 the drugs in the general population and the CYP-mediated (3A4, 2D6 and 2C19 notably) metabolism of  
214 a lot of these drugs (20).

215 Finally, some other situations required special consideration due to the immediate lethal risk and/or  
216 high amplitude of the DDI and have been found in our study: colchicin (n=1), lercanidipine (n=11),  
217 oxycodone (n=4), tadalafil (n=2), ibrutinib (n=1), hydroxyzine (n=1), quetiapine (n=1) or vincristine  
218 (n=1).

219 This study is not without any limitation. One of the main shortcomings was that there was no  
220 assessment of the clinical outcome of patients after the expert advice has been provided. Moreover,  
221 no data was available to evaluate the clinician's adherence to the pharmacologists' expert advice. This  
222 limits the significance of the results as no performance of the strategy can be provided. Another point  
223 is the weaker pharmacodynamic expertise of the network. Indeed, if TDM specialists have probably  
224 the best skills of healthcare professionals in pharmacokinetics and dosage adjustments in case of  
225 pharmacokinetics drug-drug interactions, their expertise is weaker in pharmacodynamics. Indeed,  
226 pharmacologists working in pharmacovigilance center developed expertise in anticipating the  
227 pharmacological effects of drugs when there are combined. This is, for example, particularly true for  
228 QTc prolongating drugs. Hence, a network comprising TDM specialists and specialists in  
229 pharmacovigilance appears particularly appropriate to prevent the complete drug-drug interaction risk  
230 of nirmatrelvir/ritonavir. A strategy combining both expertise would probably help taking a step in the  
231 level of expertise provided to clinicians. Finally, such frameworks aiming at helping clinicians to identify  
232 eligible patients for nirmatrelvir/ritonavir treatment and at preventing the risk of drug-drug  
233 interactions by providing dosage adjustments and other expert advice on treatment management has  
234 been proposed in France from October 2022. The French ministry of health (Direction Générale de la  
235 Santé) started a national system where pharmacology departments and regional pharmacovigilance  
236 centers were granted guiding clinicians for nirmatrelvir/ritonavir patients' eligibility and providing  
237 expert advice on treatment management. This is consistent with the Paxlovid SmPC recommending a  
238 multidisciplinary approach including specialists in clinical pharmacology to evaluate DDI risk before  
239 drug prescription (10).

240 **Conclusion:**

241 Expert advice provided by the biological pharmacology network of the SFPT allows securing the  
242 combination of nirmatrelvir/ritonavir with other concomitant drugs. Most of eligible patients to the  
243 antiviral drug can benefit from it despite the risk of drug-drug interaction. Nevertheless, more than  
244 one drug out of four require temporary discontinuation and more than one out of ten a dosage  
245 adjustment. This emphasizes the need for a pharmacological expertise to evaluate the risk of DDI and  
246 their potential clinical consequence in patients, to anticipate the DDI amplitude to adjust drug dosage  
247 and to plan treatment monitoring during combination of drugs and novel treatment adjustment at the  
248 end of the antiviral treatment.

249

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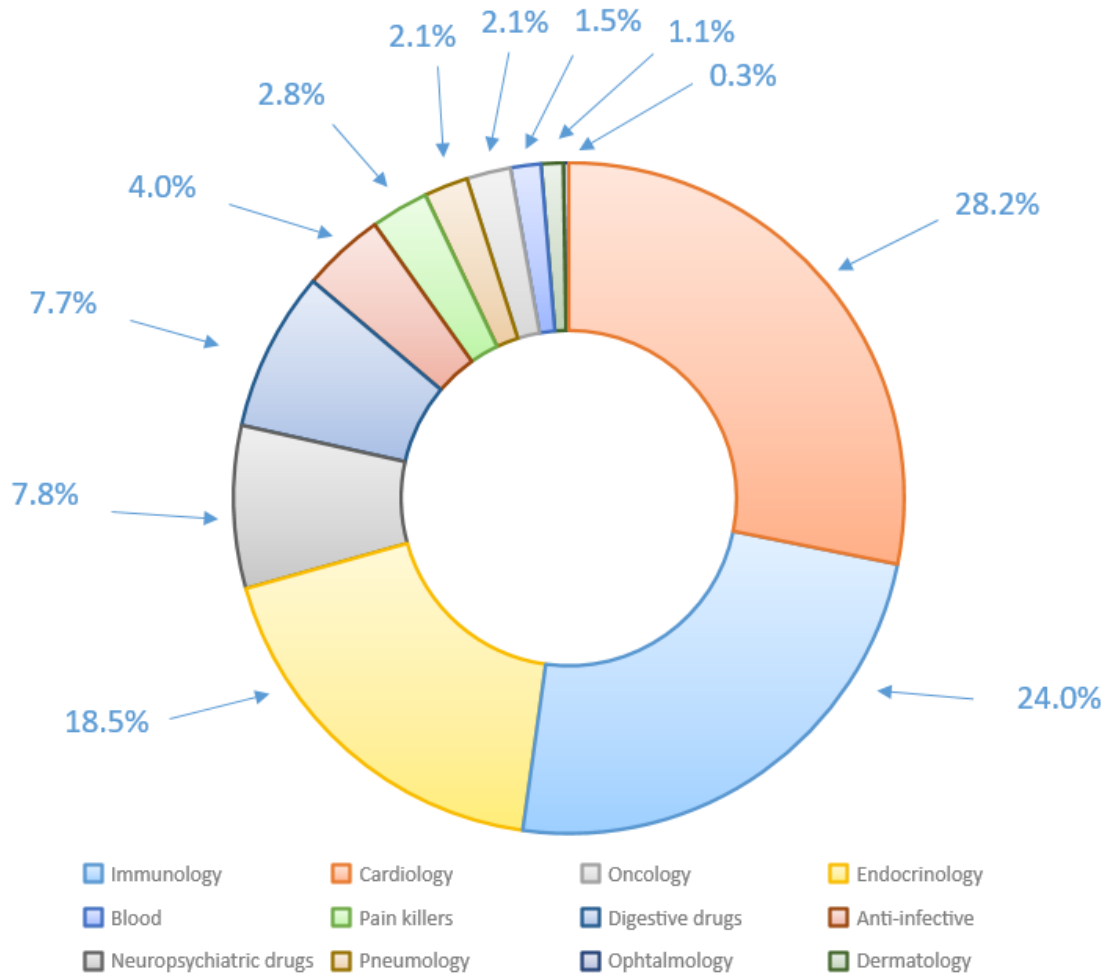
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308 **Figure legends:**

309 **Figure 1: Type of drugs benefiting from expert advice**



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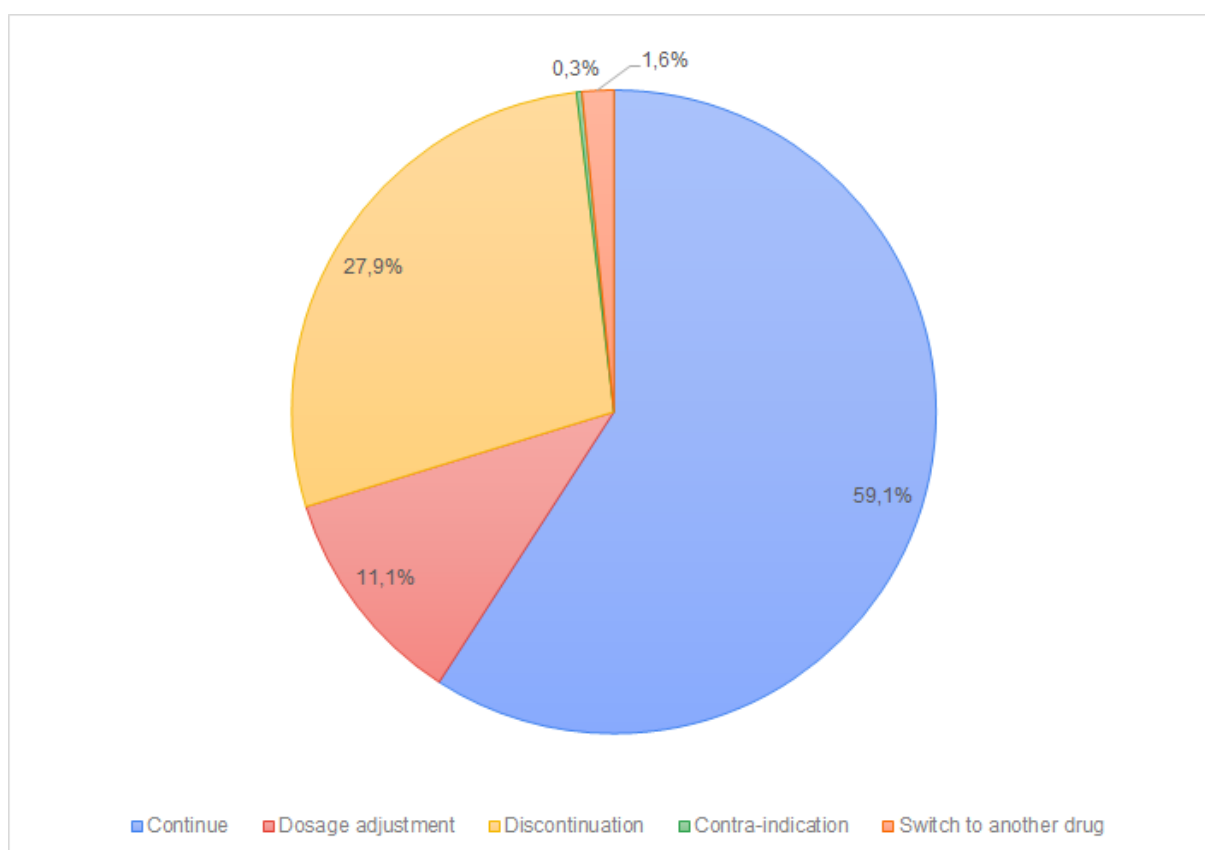
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317 **Figure 2: Therapeutic interventions proposed after expert advice**



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320 **Table 1. Thirty most common drugs advice request**

Rank	Drug	Advice provided
#1	Tacrolimus	57
#2	Mycophenolic acid	52
#3	Acetylsalicylic acid	33
#4	Atorvastatin	24
#5	Vitamin D	22
#6	Methylprednisolone	21
#7	Prednisone	19
#8	Amlodipine	17
#9	Pantoprazole	17
#10	Esomeprazole	15
#11	Furosemide	12
#12	Insulin	12
#13	Lansoprazole	11
#14	Bisoprolol	11
#15	Lercanidipine	11
#16	Perindopril	10

#17	Allopurinol	10
#18	Cotrimoxazole	10
#19	Acetaminophen	9
#20	Levothyroxin	9
#21	Metformin	8
#22	Azathioprine	7
#23	Prednisolone	7
#24	Lisinopril	7
#25	Ciclosporin	7
#26	Moxonidin	7
#27	Atenolol	6
#28	Rosuvastatin	6
#29	Everolimus	6
#30	Apixaban	6

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