GLOBAL COLLABORATION TO PROVIDE DRUG INTERACTION GUIDANCE FOR NIRMATRELVIR/RITONAVIR

NIH COVID-19 Treatment Guidelines

515

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BACKGROUND

- Nirmatrelvir/ritonavir (NMV/r, Paxlovid), a preferred antiviral for high-risk outpatients with COVID-19, is associated with major drug-drug interactions (DDIs) secondary to CYP3A4 and/or drug transporter inhibition (P-glycoprotein, BCRP).
- Initial NMV/r DDI product information was extrapolated from chronic, full-dose ritonavir use; however, some DDIs may not be relevant when using a low-dose, 5-day ritonavir treatment course (e.g. CYP2D6 inhibition or enzyme induction)
  - Of the drugs common to the EMA, FDA, and Health Canada product information, 30% of DDI management recommendations were not consistent.
- In Dec 2021, 3 international groups – University of Liverpool (UoL), NIH COVID-19 Guidelines Panel, and Ontario Science Table (OST) pharmacist contributors simultaneously developed NMV/r DDI guides to assist clinicians.
- In Jan 2022, the DDI experts from these 3 entities established a global collaboration to address DDI challenges limiting NMV/r use in real-life settings and align DDI guidance recommendations to ensure consistency and best practices.

METHODS

- In 2022, 12 virtual meetings were convened.
- Metrics were collected from the UoL DDI checker for the most searched DDIs globally and by DDI severity. 2022 usage metrics for each DDI guidance were compiled.
- Differences in recommendations between product information and DDI guides were compared.

RESULTS

- The 3 teams met monthly to discuss DDIs, review DDI literature, and achieve consensus on recommendations. Additional experts were invited as needed.
  - To factor in the lower ritonavir dose and shorter treatment duration, some recommendations differed from product information.
  - The group discussed the duration of significant CYP3A4 inhibition and appropriate timing for re-starting or re-adjusting the dose of concomitant high-risk medications.
  - The benefits of NMV/r treatment versus risk of harm due to severe DDIs, in an already high-risk population, were considered when developing guidance.
- Additional details related to the management of DDIs (e.g. duration of medication pausing, dose adjustment, clinical monitoring, patient counselling) were provided in UoL and OST DDI guides when needed.
- Categories that required the most discussion and revision included: anticoagulants, immunosuppressants, calcium channel blockers.
- Potentially clinically relevant DDIs accounted for one third of UoL DDI queries, highlighting the need for DDI guidance.
  - Query results were used to assess and respond to the needs of users by refining interpretations and/or creating extra resources (such as the OST direct oral anticoagulant algorithm).
- Utilization of DDI guides was not limited to in-country resources.

RESULTS

Table 1. Description and 2022 Metrics for NMV/r DDI Guides

	University of Liverpool	NIH Guidelines	Ontario Science Table
DDI Guide Description	Web-based, interactive DDI checker	Webpage/PDF, (outpatient focus)	Webpage/PDF (DDI table and DOAC algorithm)
Comparison of Initial Versions of DDI Guides to Product Information[1]			
No. of drugs in DDI guide vs. product information	558 (UoL) vs. 137 (EMA product label/FDA EUA FS)	68 (NIH) vs. 100 (FDA EUA FS)	133 (OST) vs. 120 (Health Canada monograph)
% of recommendations different	27%	33%	29%
Comparison of End of 2022 Versions of DDI Guides to Product Information[1]			
No. of drugs in DDI guide vs. product information	880 (UoL) vs. 177 (EMA product label/FDA EUA FS)	214 (NIH) vs. 143 (FDA EUA FS)	139 (OST) vs. 130 (Health Canada monograph)
% of recommendations different	25%	29%	32%
DDI Guide Revisions and Usage Metrics			
No. of revisions to drug entries in 2022[2]	143	37	20
No. of revisions resulting in upgrades or downgrades in severity of DDI	6 upgrades 44 downgrades	3 upgrades 23 downgrades	1 upgrade 1 downgrade
NMV/r DDI Usage Metrics for 2022	**7,082,819 NMV/r queries** (85% of all DDI queries) **NMV/r DDI queries by country:** USA: 3,499,795 (49%) Canada: 549,151 (8%) UK: 442,677 (6%)	**1,757,875 pageviews** (11% of all views on website, most viewed page in 2022) **No. of referrals to other DDI resources**: UoL: 161,478 FDA: 47,045 OST: 37,618	**244,695 DDI pageviews** (43% of all views on OST website) **Most viewed page in 2022**

Key: DOAC = direct oral anticoagulant; DDI = drug-drug interaction; EMA = European Medicines Agency; EUA FS = Emergency Use Authorization Fact Sheet for Healthcare Providers; FDA = Food and Drug Administration; NMV/r = nirmatrelvir/ritonavir; OST = Ontario Science Table; University of Liverpool (UoL)

[1] Product information refers to the product labeling, fact sheet, or monograph authorized by the relevant regulatory agency for each region or country. Product information was not uniformly consistent between regions or countries (e.g., the number of drugs addressed and/or certain DDI interpretations).

[2] Includes revisions that did not lead to changes in DDI recommendations, such as updates to evidence summaries or comments.

Figure 1. UoL NMV/r Queries by Interaction Severity (2022)

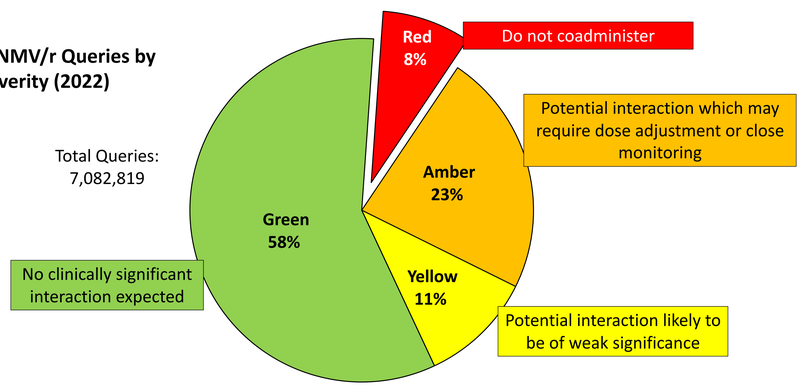


Figure 2. NIH COVID-19 Guidelines Section Pageviews (2022)

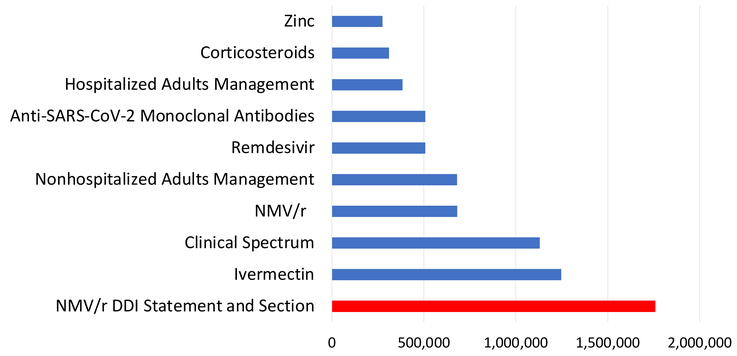


Figure 3. OST COVID-19 Science Briefs Pageviews (2022)

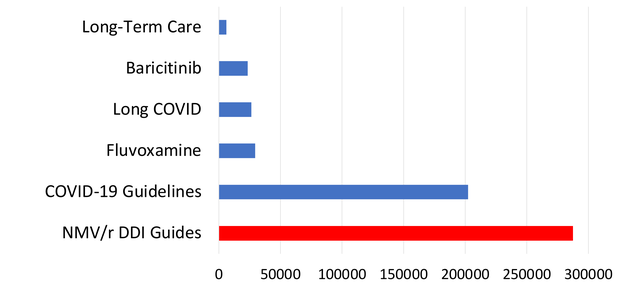
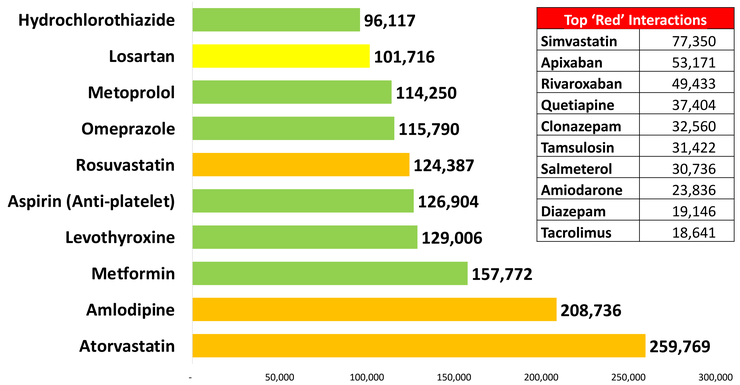


Figure 4. UoL NMV/r Top Comedication Queries (2022)



Top 'Red' Interactions	
Simvastatin	77,350
Apixaban	53,171
Rivaroxaban	49,433
Quetiapine	37,404
Clonazepam	32,560
Tamsulosin	31,422
Salmeterol	30,736
Amiodarone	23,836
Diazepam	19,146
Tacrolimus	18,641

CONCLUSIONS

Substantial efforts have been made by the 3 international teams of experts to provide up-to-date, complementary guidance for the management of NMV/r-related DDIs. Usage metrics confirm the demand for DDI guidance during the pandemic, and cross-utilization of the DDI guides confirms the need for consistency. The DDI guides were broader than product information, expanding clinicians' ability to prescribe NMV/r. DDI guidance for anticoagulants and immunosuppressants was particularly challenging. During drug development, complex DDIs likely to be encountered in target populations should be assessed. In conclusion, during the COVID-19 pandemic, this global collaboration responded quickly to the significant need for DDI guidance to facilitate the use of NMV/r.

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