Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

Vegard Myhre

Drug Combinations for Treatment of Emerging and Re-emerging Viral Infections

Development of a New Database for Antiviral Drug Combinations

Master's thesis in Molecular Medicine
Supervisor: Denis Kainov
May 2022

NTNU
Kunnskap for en bedre verden

Vegard Myhre

Drug Combinations for Treatment of Emerging and Re-emerging Viral Infections

Development of a New Database for Antiviral Drug Combinations

Master's thesis in Molecular Medicine
Supervisor: Denis Kainov
May 2022

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

NTNU
Norwegian University of
Science and Technology

Acknowledgements

No master's thesis is truly independent, and my work would not have been possible without the support of others.

My supervisor Dr. Denis Kainov has provided excellent support and inspiration, and his exceptional expertise and passion within virology made it easier to learn the ropes. His assistance, feedback, and sense of direction was also invaluable throughout my thesis. Hilde, Aleksandr, and Rouan has also provided valuable input, and especially my fellow MSc student Ronja. To all my colleagues, it has been wonderful working with you.

Finally, I will also mention my friends and family for their support during my MSc.

Thank you all,

Vegard Myhre

Publications

I was involved in two scientific publications while I was working on my thesis, and parts of my thesis are included in them. The two publications are:

Ianevski A, Yao R, Simonsen RM, Myhre V, Ravlo E, Kaynova GD, et al. Mono- and combinational drug therapies for global viral pandemic preparedness. iScience. 2022;25(4):104112

Ianevski A, Simonsen RM, Myhre V, Tenson T, Oksenych V, Bjørås M, et al. DrugVirus.info 2.0: an integrative data portal for broad-spectrum antivirals (BSA) and BSA-containing drug combinations (BCCs). Nucleic Acids Research. 2022 (In press)

Table of Contents

List of Figures

List of Tables

List of Equations

List of Supplementary Tables

Abstract

The ongoing SARS-CoV-2 pandemic is just one of many recent viral pathogens that demonstrates the need for new tools to combat emerging and re-emerging viral infections. The use of antiviral drugs is a proven treatment option that has been used as first line of defence when new viruses emerge, but antiviral drugs can be even more effective when they are administered in synergistic antiviral drug combinations (AVCs). Synergistic AVCs show higher potencies compared to monotherapies, and additionally also have the benefit of increased resistance to viral mutations. Antiviral drug development is however slowing down due to the increased difficulty of discovering new drugs, and it is also a high cost and time-consuming process. Exploration of drug repurposing, and preferentially drugs in AVCs, should therefore be prioritized to cut costs and for more rapid drug approval, which would be beneficial when faced with new viral pathogens. Predictions of synergistic AVCs based on previous experiments and clinical trials would additionally allow for more targeted approaches for AVC discoveries. But to do so require knowledge of which drug traits synergizes well together, which in turn also require a database were such data can be found. Currently the AntiviralCombi database is the only database for previously tested AVCs, but it needs refinement if it is to be used for analysis. The development of a new refined database for AVCs are therefore needed and would provide a foundation for future AVC predictions.

In this thesis I created a new database with information on previously tested two-drug AVCs in a new and standardized database, named AntiviralDualCombi (AVDC). It was created by using and standardizing the AntiviralCombi database, plus additional literature searches. AVDC features 758 two-drug AVC entries, split into 533 distinct AVCs, 337 distinct antiviral drugs, and 52 distinct viruses. AVDC was here used alone or together with DrugVirus, a database with 255 broad-spectrum antivirals (BSAs), to investigate potential beneficial AVC traits by heatmaps and statistical tests. Several beneficial and adverse traits were found, but they need to be confirmed *in vitro*. Hundreds of BSA-containing combinations (BCCs) were also discovered, and the BCCs were also added to DrugVirus in an update to the database. Finally, I participated in the development of a mathematical model for BCC predictions with my research group, where BCCs in AVDC were used as a point of reference.

Sammendrag

Den pågående SARS-CoV-2 pandemien er kun en av mange virale trusler som viser at det er behov for redskap for å bekjempe kommende og gjenkommende virusinfeksjoner. Bruken av antivirale legemidler er bevist behandlingsmetode som har vært første forsvarslinje når nye virus oppstår, men antivirale legemidler kan også bli enda mer effektive når de kombineres i synergistiske antivirale legemiddel kombinasjoner (AVC). Synergistiske AVC har høyere potens enn individuell legemiddelterapi, og har i tillegg fordelen med å være mer resistent mot virusmutasjoner. Utviklingen av antivirale legemidler går derimot saktere ettersom det blir vanskeligere å oppdage nye legemidler, og det er i tillegg en prosess med høye kostnader som også krever en del tid. Utforskningen av legemidlers sekundærbruk, og fortrinnsvis legemidler i AVCer, bør derfor prioriteres for å kutte kostnader og tiden det tar for legemiddelet godkjennes, som er fordel i møte med nye patogener. Å forutse synergistiske AVCer basert på tidligere forsøk vil tillegg legge til rette for nye AVC oppdagelser, men for å gjøre dette er det behov for en database der disse dataene kan hentes. For øyeblikket er AntiviralCombi den eneste databasen som inneholder testede AVCer, men oppføringene dens trenger raffinering om de skal benyttes. Det er derfor et behov for konstruksjonen av ny AVC-database om forutsigelser av AVCer skal være mulig.

I denne oppgaven lagde jeg en ny database kalt AntiviralDualCombi (AVDC) som inneholder informasjon om tidligere testet to-legemiddel AVCer, der databasen ble laget basert på AntiviralCombi og ekstra litteratursøk. Min nye AVDC database inkluderer 758 to-legemiddel ALK oppføringer, delt videre inn i 533 distinkte AVCer, 337 distinkte antivirale legemidler, og 52 distinkte virus. AVDC ble her brukt alene eller sammen med DrugVirus, en database om 255 bredt spektrum antivirale legemidler (BSA), for å undersøke potensielle fordelaktige AVC egenskaper med varmekart og statistiske tester. Flere fordelaktige egenskaper ble funnet, men de må bekreftes *in vitro*. Flere hundre BSA inneholdende kombinasjoner (BCC) ble også oppdaget, der de også ble opplastet i DrugVirus-databasen i en ny oppdatering. Til slutt deltok jeg i utviklingen i en matematisk modell for å forutsi synergistiske BCCer, der AVDC ble brukt som referanse.

Abbreviations

AVC	Antiviral drug combination
AVDC	AntiviralDualCombi
BSA	Broad-spectrum antiviral
df	Degrees of freedom
ICTV	The International Committee on Taxonomy of Viruses

1 Introduction

The recent and still ongoing SARS-CoV-2 pandemic has showed how unprepared the world currently is when faced with emerging and re-emerging viral infections. The most common interventions used so far to combat SARS-CoV-2 have been quarantines and social distancing, and while these measures are effective in limiting new infections, they do not help the already infected individuals already in need of treatment (1). Nor does it help hospitals and health care installations who are facing overcrowding and being overwhelmed, in addition to the cost governments and the businesses face in lost revenue and increased expenses. Quarantines and social distancing are however not new interventions, as they are common during outbreaks, but it only highlights the need of new and more effective treatments that can be rapidly deployed (2, 3). A strategy that needs to be explored further is the discovery and development of new drugs and synergistic drug combinations, which could limit the spread of new pathogens and shorten the duration of new pandemics (4).

One of the challenges in preparing for the next pandemic is identifying the pathogen that will cause it and its origin, but a pathogen of viral zoonic origin is the most likely. Estimates have shown that of 1400 pathogen surveyed, 58 % were of zoonotic origins, and viruses were the clear overrepresented group of pathogens regarded as an emerging or re-emerging threat (5). Indeed, out of the 1400 pathogens surveyed, 208 were regarded as an emerging or remerging threat, split into 77 viruses, 54 bacteria, 22 fungi, 14 protozoa and 10 helminths. It was also found that the type of genome (i.e. RNA or DNA) and positive or negative-stranded RNA viruses were not more likely to be a threat. Although if viewed numerically, RNA viruses dominated, as seen in the past with influenza viruses and other coronaviruses, possible due to the mutation rate of RNA viruses in general (6, 7). Focus should therefore be put especially

into the search for effective antiviral treatments, but it should also take the unpredictable nature of viruses into consideration (8).

Vaccines are a popular proactive measure that limit viral infections. Other options however may be better as vaccines require surveillance networks if they are to be used for preparations, and the vaccines themselves may have a narrow target range of viruses that makes them vulnerable to mutations (7, 9, 10). An alternative to vaccine development is the development of antiviral drugs, which has been an important therapeutic first line of defence when no vaccines have otherwise been available (9, 11). The first antiviral to be discovered was idoxuridine in 1961 for hepatitis C, which later in 1963 was also approved for the treatment of Herpes simplex virus 1. Since then, over 90 antiviral drugs been approved targeting a variety of viruses and drug targets (12, 13).

A group of antiviral drugs named broad-spectrum antivirals (BSAs) was identified early as antivirals able to target several viral pathogens from different viral families, and this ability makes BSAs beneficial for pandemic preparations (14-16). BSAs targets common pathways and features of viruses and are thus prime candidates for targeted drug repurposing (17). For instance, the U.S. Food and Drug Administration gave the BSA remdesivir an emergency approval during the SARS-CoV-2 pandemic, demonstrating once more the use of antiviral drugs for targeting new threats, but also the potential for BSAs (18). Common targets for BSAs include nucleoside-, nucleotide-, and pyrophosphate analogues, in addition to inhibitors targeting reverse-transcriptase, integrase or protease inhibitors, but antiviral drugs may also have host targets. Although host targets can be a double-edged sword, with potential benefits such as more tolerance for virus mutations, but with potential adverse effects such as disruption of normal cellular processes. There are several host targeting antivirals, and one group is the immunomodulatory drugs. They can be beneficial where pathogens avoid the host immune system, the pathogen modify the immune system to the benefit the pathogen, or the pathogen increases the damage the immune systems damage does to the host (19). However immunomodulatory drugs can also have its downsides and result in autoimmunity, cytokine storms, and reduced response for the adaptive immune system (20, 21).

One limitation when it comes to antiviral drugs is their development and costs. Drug development normally takes 13-15 years from initial testing until it reaches the market, with costs in the range of two to three billion US dollars (22). The estimated probability for a drug

to be approved after clinical phase I is also around 14 %, with the bottleneck being able to advance past phase II (23). Not only is drug development a time- and resource heavy process, but drug approval rates are also slowing down, and it gets increasingly difficult to discovered new drugs. Other options should be investigated, and drug repurposing would limit these downsides of traditional drug development. Drug repurposing uses already approved drugs to treat additional pathogens, other than its original target, which would reduce the financial burden and speed up development. Idoxuridine, the first antiviral drug, was for instance originally an antitumour before its repurposing as an antiviral (24). Using already tested drugs can arguably skip phase I of clinical testing, and may save 300 million US dollars and 6.5 years of development. It Is therefore not surprising to see that there is a shift from development towards drug repurposing (25, 26).

Drug candidates for drug repurposing can be found by several strategies, but two common methods are by target-based repurposing and by *in silico* assisted repurposing (27). In target-based repurposing, drug candidates are identified by looking at the drug targets and pathogens susceptible the target or finding new targets for drugs that were previously unknown. Another strategy is the development of *in silico* methods that rely on extended literature analysis and data mining to assist in discovering drug and pathogen relationships, in addition to model constructions.

Another consideration is that while monotherapies with one antiviral drug may be effective, the administration of two or more synergistic drugs in combination therapies has several advantages compared to monotherapy. The potency for antiviral drugs can be increased past their original levels when they are administered in drug-cocktails, which reduces the required dosage and toxic effects. Another factor is the forementioned unpredictable nature of viruses and their mutations, and by using drug cocktails it decreases the chances of a virus developing drug resistance towards it (28). Combination treatments has also been the standard for hard-to-treat viruses such as hepatitis C and human immunodeficiency virus, where combination treatments also being available as salvage treatments (29, 30). With the SARS-CoV-2 pandemic, very few monotherapies got approved for treatment, and the development of effective combination therapies for rapid deployment could be the solution for future pandemics (31). Thus, a beneficial strategy in preparing for new emerging and re-emerging viral infections will be using already known drugs in repurposing, and in combination therapies.

However, while there are many experiments on combination therapies already published, there are limited resources and databases available to summarize these experiments and to be used for analysis. There are also limited data on beneficial and adverse traits of individual drugs that may impact its use as components in antiviral drug combinations (AVCs), although some are known. Drugs with similar targets may compete, especially the nucleoside/nucleotide analogues, and they often have adverse effects (32). Other traits, such as immunomodulatory properties, may also interfere with each other if they are similar.

The first, and currently only, database to summarize tested drug cocktails has been the AntiviralCombi database, launched in 2020 by my research group as a freely accessible database (33). It summarized 985 antiviral drug combinations (AVCs) and their developmental status, in addition to the AVCs targeted viruses. While the database itself was an excellent steppingstone towards a comprehensive lexicon of combination data, the data itself was lacking a standardize format and would need an update if it were to be used for analysis. Its update to a standardized format and expansion will therefore be the primary aim in my thesis, as it could reveal beneficial traits for AVCs. Although the database will be transformed into a new database called AntiviralDualCombi (AVDC) with just two drugs per AVC for simplification. This simplification will allow for easier statistical and *in vitro* tests in the future, in addition to that fewer drugs in an AVC decreases the chances of toxicity (34).

The DrugVirus database was also launched in 2020, and summarized initially 120 BSAs able to inhibit several different viral families (14). The database included data on the BSA drug targets, their immunomodulatory properties, and their approval status. The DrugVirus database was recently updated and expanded to 255 BSAs, and with this expansion it could be further used together with the AVDC database for analysis of successful two-drug AVCs (35-37). The analysis could reveal beneficial and adverse traits of BSA-containing drug combinations (BCCs), who can expand the range of data included in DrugVirus. BCCs has also the advantages of BSAs with the added positive effects of combination therapies, such as increased resistance to viral mutations and increased drug potencies if synergistic. Their identification and testing could return valuable new insight and drugs when faced with new pandemics (38), especially if in silico and mathematical models can be developed in preparation for the next pandemic (39). The use of AVDC with DrugVirus and BCC identification and model predictions, will therefore also be an aim for this thesis.

2 Research aims

There is a need for more rapidly deployed treatments when faced with emerging and re-emerging viral infections. While vaccines are an effective proactive treatment prior to infection, it does not treat already infected patients. The more active alternative would be using antiviral drugs, where antiviral combination therapy has been shown superior in many cases. The inclusion of broad-spectrum antivirals (BSAs) in the antiviral drug combinations (AVCs) would also be beneficial for targeting a wider range of different viruses.

Currently there are no mathematical or *in silico* approaches that can be used in the prediction of new AVCs, but to do so a reliable database is needed as a foundation. My thesis aims at creating a new database, AntiviralDualCombi (AVDC), based on the AntiviralCombi database, although with standardized formats and limited to two-drug AVCs. Two-drug AVCs will be easier to test statistically and *in vitro* and will be an important first step which later can be expanded upon. Also, if the database is standardized, it would allow me to use additional data from other databases for further analysis and statistical test. These analysis and test could then reveal beneficial traits for successful two-drug AVCs, while also revealing negative ones.

Here I will use my new database with the DrugVirus database as a proof of concept, where it will be a secondary aim of the project. Some basic statistical testing will be performed which may reveal beneficial or adverse traits of AVCs able to enter clinical trials. Another aim for my project will be the update and addition of BCCs in the DrugVirus database, where the updated AVDC data can be used with mathematical models for predictions of new BCCs. Finally, I will work with my research group to develop a mathematical model for BCC predictions.

3 Materials and Methods

Microsoft Excel 365 was used often in this thesis. While formulas are explained during their uses in this section, readers are also encouraged to read the summary and explanations of all formulas used in this thesis in the supplementary (Supplementary Table A).

3.1 Creating a new database

3.1.1 Filtering AntiviralCombi for two-drug antiviral combinations

The database AntiviralCombi was downloaded from AntiviralCombi.info as csv-file with all its 985 entries (40). All entries had three columns for the drugs used in the antiviral drug combinations (AVCs) (note that a column could include more than one drug), a column for targeted virus, a column for entered clinical stage, a column for model (e.g. cell lines, animals), a column for tissue/organ for the cell lines, a column for reference, and a final column with a link to its entry on the website.

The data was loaded into Microsoft Excel 365 and converted into a table. All entries were inspected manually, and if a cell in an entry had more than one drug, the drugs were separated by a semicolon. When all entries were inspected, the three drug containing columns were merged into one, but with a semicolon added where the next column would have started. This resulted in all individual drugs being separated by a semicolon and listed in a single column.

The now single drug column was analysed using Excel Power Pivot. In Power Pivot each cell was split into multiple columns, filtered by the semicolons used to separate the individual drugs. The resulting table included seven columns total, representing that the highest number of drugs found in a single AVC was seven. Thus, if a drug combination only had two drugs included in the AVC, the next five columns would be empty. By then only extracting entries without any characters in these next five columns, the AntiviralCombi database was filtered from 985 multiple-drug AVCs to 704 two-drug AVCs, removing 30 % of the initial database.

3.1.2 Drug name standardization

The AntiviralCombi database used both brand- and generic names in their entries, and the next step was to standardize their names into a single format. Generic names were chosen for convenience for future literature searches. The UNIQUE formula in Microsoft Excel 365 was used to identify distinct drug names in the database, as it is a powerful tool to summarize tables. The UNIQUE formula filters a dataset by rows or columns using unique or distinct values/entries, and here UNIQUE with the distinct setting was used to extract all drug names from the database (Figure 1).

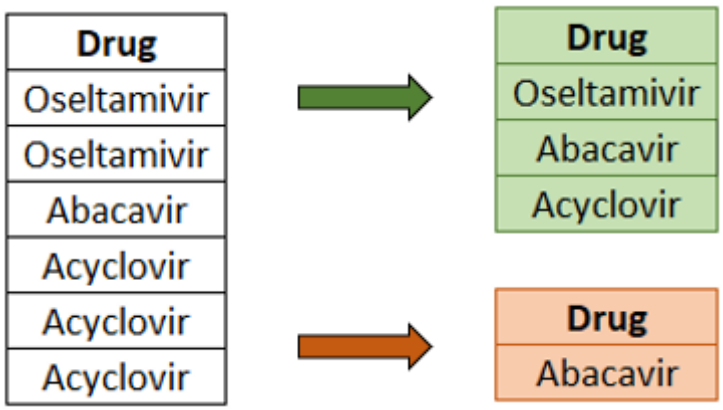

Figure 1: Data filtering using the UNIQUE function, and the important distinction of the terms "unique" and "distinct" values in a dataset. When a dataset (white, left) is filtered with the UNIQUE function set to distinct, it returns all entries but removes extra duplications (green, top right). If the UNIQUE function is set to unique, only entries that appear exactly once is returned (red, bottom right). Here an array with only one column is shown, although UNIQUE can use larger arrays.

Each distinct drug was then manually searched on the DrugBank website and corrected for generic names. DrugBank is an online database with information on generic names and their synonyms, in addition to manufacturers, drug developmental phase, pharmacology, with more (41). An additional benefit of using DrugBank was that it was also used as the reference for the DrugVirus database, which was used later.

Some drugs got merged as they do not have a fixed molecular structure, and/or has the same target: Peginterferons and other types of interferons were merged into four categories; interferon alpha, beta, gamma, and lambda. Different kinds of antibodies, siRNAs and miRNAs was also merged into their respected categories.

3.1.3 Virus name and clinical phase standardization

The database was here standardized for virus abbreviations and clinical phases.

To standardize virus abbreviations, the DrugVirus database was downloaded from DrugVirus.info, and its abbreviations were used as a reference (42). The UNIQUE function was used to identify distinct abbreviations in the AntiviralCombi database, and logic formulas in Excel were used to identify if a given abbreviation deviated from the DrugVirus format. Such deviations were then corrected.

All distinct categories of clinical phases in AntiviralCombi were identified using the UNIQUE function. Case studies with humans and phase 0 tests were listed as either "not applicable" or blanks in the original AntiviralCombi database, and they were here changed to "phase 0/1" as they had been tested in humans. Substages (e.g. phases 2a and 2b) was changes to their main stage (i.e. phase 2). "In vitro" and "in vivo" was changed to "preclinical".

3.1.4 Standardization of drug order

The AntiviralCombi database did not have a standardize format for sorting the order in which the drugs were listed. The order would later be important for identifying and removing duplicate entries, and thus they needed to conform to single format throughout the new AVDC database. To achieve this, alphabetical sorting of the two drugs were chosen for convenience.

The formulas INDEX, MATCH, and COUNTIF was used to automatically sort the AVCs. The INDEX formula returns the value at a specific coordinate in a dataset/array. The MATCH formula returns the position of a lookup value in an array, and COUNTIF returns the number of cells in an array that meet a set criterion. An in-depth explanation is listed below (Table 1). By setting up a formula made from these components, both drugs per combination were sorted alphabetically.

Table 1: In-depth explanation of the formulas used to alphabetically sort the two drugs per AVC. The drugs were in the same rows but in different cells (i.e. different columns). Note that the dataset was treated as a table which also reflect the formulas.

Function	Formula
Component. Returns the alphabetical position of two drugs in the same row in a table as an array. A returning [2,1] array would indicate that the second drug comes before the first drug alphabetically, while an [1,2] array would indicate the first drug comes first.	COUNTIF(Table[@[Drug1]:[Drug2]];"<="&Table[@[Drug1]:[Drug2]])
Component. Returns the first number in the COUNTIF array.	MATCH(1;COUNTIF(Table[@[Drug1]:[Drug2]];"<"&Table[@[Drug1]:[Drug2]]);0)
Component. Returns the second number in the COUNTIF array.	MATCH(2;COUNTIF(Table[@[Drug1]:[Drug2]];"<"&Table1[@[Drug1]:[Drug2]]);0)
Final formula. Retrieves the alphabetically first drug name from each row. The formula can also be seen as converting the number found in COUNTIF to a drug name using INDEX and MATCH.	INDEX(Table[@[Drug1]:[Drug2]];MATCH(1;COUNTIF(Table[@[Drug1]:[Drug2]];"<="&Table[@[Drug1]:[Drug2]]);0))
Final formula. Retrieves the alphabetically second drug name from each row. The formula can also be seen as converting the number found in COUNTIF to a drug name using INDEX and MATCH.	INDEX(Table[@[Drug1]:[Drug2]];MATCH(2;COUNTIF(Table[@[Drug1]:[Drug2]];"<"&Table[@[Drug1]:[Drug2]]);0))

3.1.5 Expanding and updating AntiviralCombi

With the drugs, viruses, and clinical stage formats now standardized, I continued with updating and expanding the database. The removal of AVCs with more than two drugs had left the current database with 704 entries (3.1.1 Filtering AntiviralCombi for two-drug).

Updating existing entries were conducted using "([Drug1]) AND ([Drug2]) AND (Combination)" as queries in manual searches on the US National Library of Medicine website PubMed.gov, the search engines Web of Science and Google scholar, and in their original published website (e.g. ClinicalTrials.gov from the U.S. National Library of Medicine, Chinese Clinical Trial Registry). If an AVC had begun testing in a higher clinical phase, then the previous entry was updated. All individual 704 AVCs from the now standardized database were searched individually, and new combinations were also found while doing these searches.

Additional manual literature searches were performed by using PubMed, Web of Science and Google Scholar. "Combination therapy", "Synergistic drugs", "Drug combination therapy", and "synergistic antiviral drugs" were used as queries. Thousands of articles were inspected, and after the new entries had underwent the same standardizations as mentioned earlier (3.1.2, 3.1.3, 3.1.4), 80 additional entries were added to the database, prior to removal of duplicates.

3.1.6 Removal of true duplicates and the finalized database

If the new AVDC database are to be used for identification of beneficial traits and statistical testing, it is crucial that duplicate entries are removed as to not inflate the data. It is also however crucial to keep a record of cell cultures used in preclinical trials, as different cell cultures can give AVCs different results, and could therefore be useful for researchers (43). The solution to this conflict of interest was here solved by keeping all entries of preclinical trials with different cell cultures or animal models, even though they had the same AVC and target virus, and to remove all entries with lower clinical phases if they have an entry with a higher phase and similar AVC and target virus. But while these lower clinical phase entries were removed, their reference was kept by transferring and adding it to the entry with the higher clinical phase, as not to lose any data. Future researchers interested in these entries can therefore still use the data by separate them using methods described earlier, with UNIQUE and PowerPivot (3.1.1).

The removal of duplicates was performed using the COUNTIFS formula, a formula who counts cells in an array given by a set of criteria. Here the criteria were set to the AVCs and their targeted virus. By then sorting entries by their returned COUNTIFS value, and handle duplicate entries as just described, the entire database was corrected for any duplicates. Thus, the AntiviralCombi database had been fully transformed into the new AVDC database. Drug and virus frequencies in this new database was further investigated using UNIQUE with the distinct setting to identify all individual antiviral drugs and viruses, and then COUNTIF to count their occurrence in AVDC.

3.2 Creating a heatmap

Visualization of my new AVDC database would allow a two-dimensional view of the database, which can be used with other databases to look for visual clues of beneficial traits to AVCs. This heatmap would later be used to visualize data from DrugVirus database. A visualization would however limit somewhat the information showed from the database, and what data to show was therefore needed to be considered. Here I wanted the visualized data to show AVCs tested with their highest clinical phase entered, as an indication of the success of the individual AVCs. I also wanted the number of distinct viruses tested per AVC to also be visualized, as it represents the diversity tested by a given AVC. As the AVDC database was created in Microsoft Excel 365, this platform for also chosen for creating the heatmap.

3.2.1 Generating heatmap axis

The heatmap axis was first needed to be made before the AVDC data could be converted from a table to a two-dimensional heatmap. The axis was set up to be all the distinct antiviral drugs in AVDC, and the UNIQUE function with the distinct setting was used to retrieve all 335 individual drugs from the database. The drugs where then sorted alphabetically and used as the axis.

3.2.2 Finding distinct number of viruses tested per combination

I wanted the heatmap to show how many distinct viruses a given AVC had been tested on. To do this, a helper column was added to the AVDC database and filled with the formulas ROWS, UNIQUE, and FILTER. (Table 2). FILTER filters and returns an array based on

given criteria, so by using the AVCs as filters, it returns an array of all entries in my database of a particular AVC. This array can then again be filtered using the UNIQUE function to only return an array of distinct viruses per AVC. Finally, the ROWS function counts the number of rows in that array, thus giving the number of distinct viruses tested by a given AVC.

Table 2: Explanations of formulas used to retrieve number of distinct viruses tested by a given AVC.

Explanation	Formula
Component. Filters the AVDC database and returns an array that must include the same AVC as the AVC sharing the same row as the as the formula.	FILTER(Table[[Drug1]:[Virus]];([Drug1]=[@Drug1])*([Drug2]=[@Drug2])
Final formula. Uses the UNIQUE function to retrieve the array corresponding with all viruses tested on a given AVC, found by using FILTER. The ROWS function then converts the array to a number, who then represent the number of distinct viruses tested by a given AVC.	ROWS(UNIQUE(FILTER(Table[[Drug1]:[Virus]];([Drug1]=[@Drug1])*([Drug2]=[@Drug2]);0);FALSE;FALSE))

3.2.3 Finding the highest clinical phase entered per combination

I also wanted the heatmap to include the highest clinical phase entered of a AVC, regardless of the number of viruses it has been tested on, as mentioned earlier. With the entries for clinical phases now standardized in AVDC, I could use a helper column and the IF function to convert the text strings of clinical phases (i.e. preclinical, phase 0/1, phase 1, phase 2, phase 3, phase 4) into numbers. By giving each entry their own clinical phase value, where a higher clinical phase returned a higher phase number, I could then use an additional helper column and MAXIFS to retrieve the highest clinical number per AVC. MAXIFS is a formula that returns the highest number in an array based on multiple criteria, which here was the highest clinical phase number, and the criteria being the AVCs. By then using a third column and an additional IF function, the value retrieved from MAXIFS was convert back to text string using the IF function again (i.e. from value to clinical phase in text). The highest clinical phase entered per combination, regardless of virus, was thus found for all AVCs.

3.2.4 Creating the heatmap

With axis set up and the data on distinct viruses and highest clinical phase entered per AVC ready, I could then create the heatmap. To achieve this, I would need an efficient formula that could be copied to all the 112 225 cells in the heatmap, given its size of 335 drugs in each axis.

First, I created a copy of AVDC with all entries duplicated, but where the duplicate entries had switched the position of the two antiviral drugs. This approach overcome a limitation with INDEX and MATCH, as if the reference array is without mirror AVC entries (i.e. "amantadine with adefovir" is a mirror of "adefovir with amantadine"), only half of the heatmap will be shown (Figure 2). A simple solution is therefore to duplicate all entries but with mirrored combinations. As the helper columns of highest clinical phase and number of viruses per combination are based on the UNIQUE and MAXIFS formulas, their numbers will be unaffected by the new duplicate mirror entries.

	Column nr	**1**	**2**	**3**	**4**
Row nr	**Drug**	**Acyclovir**	**Adefovir**	**Alisporivir**	**Amantadine**
1	**Acyclovir**	N/A			
2	**Adefovir**		N/A		
3	**Alisporivir**			N/A	
4	**Amantadine**				N/A

Figure 2: Demonstration of a limitation with the INDEX and MATCH formula, as they are sensitive to the numbers for its returned row- and column-number. In the case for amantadine and adefovir in the simplified heatmap shown here as an example, it has two mirror coordinates: adefovir with amantadine [2,4], and its mirror amantadine with adefovir [4,2] (dark green and dark blue, respectively). If the array INDEX uses for reference is without both these mirror combinations, only one of the two mirrors will be retrieved. Thus, if the AVDC database was kept without mirror combinations, using INDEX and MATCH will only return half of the heatmap be default (green or blue area).

The final formula used for the heatmap was set up to first retrieve the highest clinical phase corresponding to the AVC on made from the heatmap axis, and then add the number of distinct viruses per AVC in parenthesis (Table 3). A combination of INDEX, MATCH and IFERROR was primarily used for this purpose. Finally, some colour coding was added using Excel's Find and Replace tool, with colour depending on the highest clinical phase the AVC had entered.

Table 3: Break down of formulas used to construct the heatmap from the copy of the AVDC database with mirrored drug positions. As the heatmap included 112 225 cells in it, the formula needed to be able to be copied to other cells, and the formula here is specific for cell B2.

Explanation	Formula
Component of the first and second formula. Used to find the row-number in the copy of AVDC database where the drug combination is located. The combination is given by the drug at the column and row. If there are no combination in the database, MATCH returns #ERROR.	MATCH(1;(B$1=Table[[Drug1]:[Drug1]])*($A2=Table[[Drug2]:[Drug2]]);0)
First formula. INDEX is used to retrieve the highest clinical phase used by the combination, found by MATCH. [MaxPhaseTXT] was the name given to the helper column showing higesht phase. IFERROR was used to return no text if MATCH returned #ERROR.	IFERROR(INDEX(Table[[MaxPhaseTXT]:[MaxPhaseTXT]];MATCH(1;(B$1=Table[[Drug1]:[Drug1]])*($A2=Table[[Drug2]:[Drug2]]);0));"")
Second formula. Adds a " (" before the formula begins, and then returns the number of distinct viruses retired by MATCH corresponding to the drug combination. [n of virus] was the name given to the helper column showing number of distinct viruses. Then a ")" is added. IFERROR was used to return no text if MATCH returned #ERROR.	&" ("&IFERROR(INDEX(Table[[n of virus]:[n of virus]];MATCH(1;(B$1=[[Drug1]:[Drug1]])*($A2=Table[[Drug2]:[Drug2]]);0));"")&")"
Final and used formula, based on the first and second formula. An IF formula is also included to return "N/A" if the individual drug on the axis happens to be the same for the given cell.	IF(B$1=$A2;"N/A";IFERROR(INDEX([[MaxPhaseTXT]:[MaxPhaseTXT]];MATCH(1;(B$1=Table[[Drug1]:[Drug1]])*(!$A2=Table[[Drug2]:[Drug2]]);0));"")&"("&IFERROR(INDEX(Table[[n of virus]:[n of virus]];MATCH(1;(B$1=Table[[Drug1]:[Drug1]])*($A2=Table[[Drug2]:[Drug2]]);0));"")&")")

3.3 Using the new AVDC database with the DrugVirus database

The new AVDC database included two-drug AVCs and their target viruses, but without additional information on the antiviral drugs and viruses very little can be used to predict new and effective combinations. Additional databases are therefore needed to reveal patterns and traits of successful AVCs, and here AVDC was used together with the DrugVirus database for this purpose. The DrugVirus database is a freely accessible database including 255 BSAs, and includes information regarding the BSAs drug targets, immunomodulatory properties, and approval status.

3.3.1 Combining AVDC with DrugVirus

A copy of the AVDC database was created, and the DrugVirus downloaded earlier was used (3.1.3). INDEX and MATCH were used to link drug data from DrugVirus to each entry in the AVDC database for further analysis.

3.3.2 Drug targets and heatmap

With a heatmap being constructed for AVDC, it can serve as a foundation for visualization of additional data. Here it was used for visualizing AVC drug targets as a demonstration of its usefulness, but a prerequisite was that the AVC also was a two-BSA BCC, as DrugVirus is limited to data on BSAs.

In DrugVirus a BSA can have multiple targets, so the drug targets needed to be split if they were to be used as axis for the new heatmap. Each BSA with two or more targets got split into additional entries in a copy of DrugVirus, so that the BSAs could appear multiple times but with only one drug target per entry. The drug targets and their BSAs were then sorted alphabetically and used as heatmap axis. INDEX and MATCH were then used to find and visualize AVCs by using the AVDC heatmap as a reference for INDEX, and by using the drugs on the axis as criteria for MATCH. By using the AVDC heatmap as a reference directly, the limitations of INDEX and MATCH described previously was completely avoided.

3.3.3 Statistical testing

Statistical testing can be performed on AVDC alone or together with the DrugVirus database that may reveal beneficial traits for AVCs. Statistical testing was performed using Pearsons Chi-square of independence, with post hoc adjusted residual analysis. The aim of the statistical testing was not to prove statistical relationships directly, but rather to identify traits of interest that may be used for later models and *in vitro* experiments.

The Pearsons Chi square of independence tests for independence between two or more categorical variables in a contingency table with size $i \times j$ (44, 45). The test returns a Chi squared statistic based on the sum of a contingency table's residuals squared, divided by their expected values (Equation 1). The statistic can further be converted to a p-value by comparing it with a chi-squared distribution, where the degrees of freedom is equal to $(i - 1)(j - 1)$.

Equation 1

$$\chi 2 = \sum \frac{(n_{ij} - \hat{\mu}_{ij})^2}{\hat{\mu}_{ij}}$$

A post hoc analysis of the contingency table is useful for identifying cells that contribute the most, or at all, to the chi-squared statistic, and it can therefore be used to compare individual cells (i.e. individual variables). Adjusted residuals return a two tailed *z*-value by dividing a cells residual by its standard error, equal to its expected value multiplied by one minus its corresponding marginal proportions (Equation 2).

Equation 2

$$\frac{n_{ij} - \bar{\mu}_{ij}}{\bar{\mu}_{ij}(1 - p_{i+})(1 - p_{+j})}$$

The AVDC dataset includes duplicate entries when it comes to AVCs and preclinical trials, as mentioned earlier (3.1.6), and these were removed before the statistical tests. The removal was performed using UNIQUE set to the distinct setting, and by using AVCs, viruses, and clinical stages, as criteria. Statistical testing was then performed using Microsoft Excel 365.

3.4 Updating DrugVirus with BCCs, and BCC model predictions

3.4.1 Updating DrugVirus with BCCs

AVDC being used together with DrugVirus also showed which and how many AVCs in AVDC that included at least one BSA in BCCs. This data was extracted and used to update the DrugVirus database to include BCCs, as part of a major update to the database. Also included in the update was the addition of new BSAs to the database.

3.4.2 BCC model predictions

A scoring system was developed by my research group to make a model for BCC predictions. The scoring system was made of six components at the individual drug stage, with components for structural-activity relationship, drug developmental status, drug target relevance, drug immunomodulatory properties, drug route of administration, and viral phylogeny for drug repurposing to related viruses. Drugs with a high individual score was then combined with other high scoring drugs in a two-drug combination, with scoring components for drug interaction by mode of action, the two drugs human or viral targets, the drugs targeted stage of viral replication, and finally route of administration. A more detailed rundown of the scoring is in the original article (38). My contribution was mainly within the expansion of virus phylogeny, drug routes of administration, and the AVDC database.

Virus phylogeny needed to be expanded as DrugVirus only included virus abbreviations and viral family names in its dataset, and additional taxa were needed if a phylogeny component were to be included. The International Committee on Taxonomy of Viruses (ICTV) is the international recognized organization for viral taxonomy, and their taxonomic website was used initially find just viral species to each virus in DrugVirus (46). The publicly available ICTV master species list was then downloaded, where the viral specie was used as reference point to INDEX and MATCH to fill out all the other taxa to the viruses (47).

Routes of administration for the individual drugs were needed for later use when the two-drug AVCs were to be scored. The UNIQUE function was used to find distinct drugs from both the AVDC and DrugVirus databases, and these drugs where manually searched in DrugBank for available routes of administrations. The AVDC database was used later as reference when the

two-drug combinations were scored and investigated, as the BCCs in AVDC had been identified.

4 Results

4.1 Creating a new database

The original AntiviralCombi database included 985 entries, split into entries with two or more antiviral drugs per AVC, and without much standardization. Extracting two-drug AVCs using Microsoft Excel 365 resulted in 704 two-drug AVCs, and these entries were then standardized for drug and virus names. Additional literature searches increased entries up by 54, resulting in the finalized database AntiviralDualCombi (AVDC) including 758 entries. These entries were at different clinical stages (Figure 3), and could be further split into 670 distinct AVCs and target viruses, 533 distinct AVCs (excluding target viruses), 52 distinct viruses, and 337 distinct antiviral drugs.

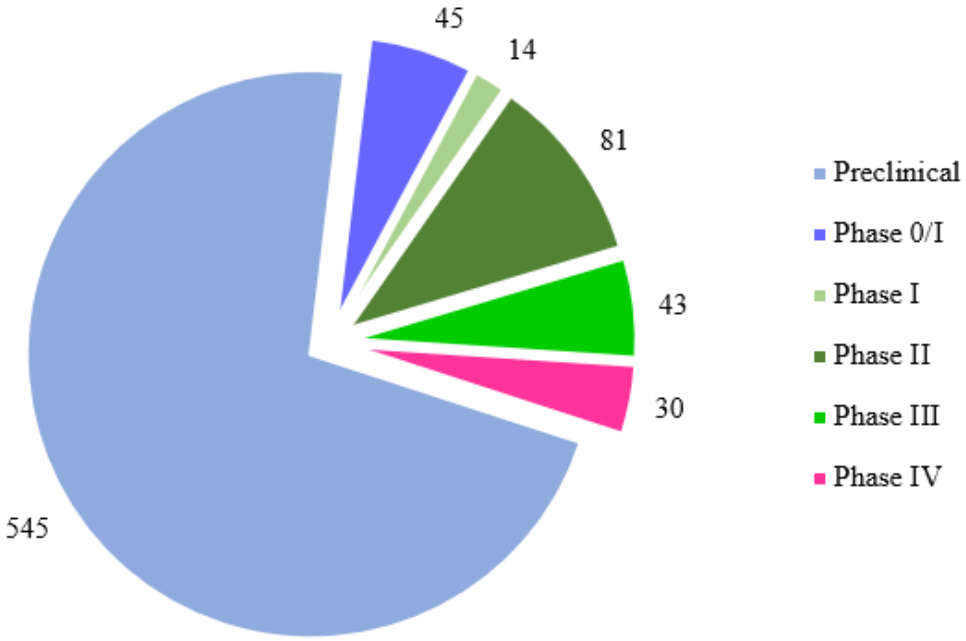

Figure 3: Summary of clinical phase distribution of all 758 combinations included in AVDC. Numbers represent counts of clinical phase in the database.

The AVDC database was also investigated for drug and virus frequencies in the database. While there can only be one clinical phase reported per entry in the database, there are two drugs per AVC. To avoid confusion the term “entry” will here be avoided and “drug slots”

used instead, as the AVDC included 758 entries having two available drug slots each, to a total of 1516 drug slots. A given drug can only be included once per entry, and thus one given drug cannot occupy more than 50 % of all drug slots in the database.

While investigating drug frequencies in the AVDC database it was found that in general, drug frequencies seemed to follow an inverse proportional pattern. 157 drugs of the 335 total drugs in the database was just included once, and sequential drug slot inclusions gradually fell off (Figure 4). It was observed that the 25 most used drugs in terms of drug slot participation accounted for 49.7 % of all drug slots in the database (Table 4). With such high participation in the database these 25 drugs were looked at even closer, and it was seen that they were included in the majority of the combinations that had entered clinical phase III and IV (Table 5). Additional break down of the top 25 drugs by drug frequency and clinical phases is in supplementary (Supplementary Table B).

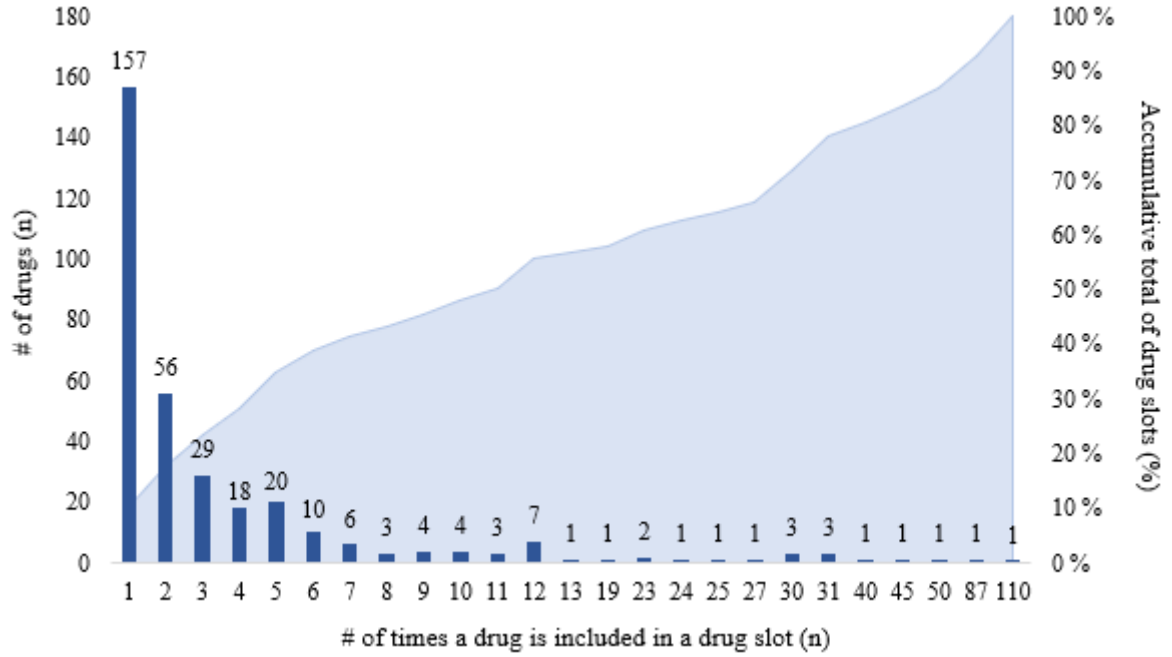

Figure 4: Visual representation of drug frequency in AVDC. Columns (dark blue) show distribution of drugs based on how many drug slots they occupy in AVDC. Background area (light blue) show accumulative percentage of drug slots in AVDC taken.

Table 4: Top 25 of 335 drugs in AVDC ranked by number of drug slots they occupy. In total, the top 25 drugs are included in half of all drug slots for AVDC combinations.

Drug	# of drug slots with the drug in AVDC	% of all AVDC drug slots
Ribavirin	110	7.3 %
Interferon alpha	87	5.7 %
Antibodies	50	3.3 %
Acyclovir	45	3.0 %
Oseltamivir	40	2.6 %
Interferon beta	31	2.0 %
Sofosbuvir	31	2.0 %
Zidovudine	31	2.0 %
Favipiravir	30	2.0 %
Foscarnet	30	2.0 %
Tenofovir	30	2.0 %
Ganciclovir	27	1.8 %
Lamivudine	25	1.6 %
Cidofovir	24	1.6 %
Interferon gamma	23	1.5 %
Ritonavir	23	1.5 %
vidarabine	19	1.3 %
Nitazoxanide	13	0.9 %
Alisporivir	12	0.8 %
Artesunate	12	0.8 %
Daclatasvir	12	0.8 %
Entecavir	12	0.8 %
Ledipasvir	12	0.8 %
Mycophenolic acid	12	0.8 %
Rupintrivir	12	0.8 %
Total	**753**	**49.7 %**

Table 5: Summary of drug slot break-down of the 25 most frequent drugs by drug slots.

	Pre-clinical	Phase 0/1	Phase I	Phase II	Phase III	Phase IV	Total
Drug slots. total	1090	90	28	162	86	60	1516
Drug slots by the 25, #	536	46	9	76	47	39	753
Drug slots by the 25, %	49.2 %	51.1 %	32.1 %	46.9 %	54.7 %	65.0 %	49.7 %

The virus frequency in the database was seen to be dominated by certain viruses. The virus frequency distribution followed an inverse proportional pattern like the drugs, but here the "right hand tail" of the distribution was longer and thus included more viruses (Figure 5). 10 out of the total 52 viruses in this database was present in 536 of the 758 total entries, giving them a substantial participation of 70.7 % (Table 6). While these viruses participated heavily in the database, they were not investigated further like the 25 most frequent drugs were, as the DrugVirus database used together with AVDC in this thesis is limited to just drug traits and not viruses.

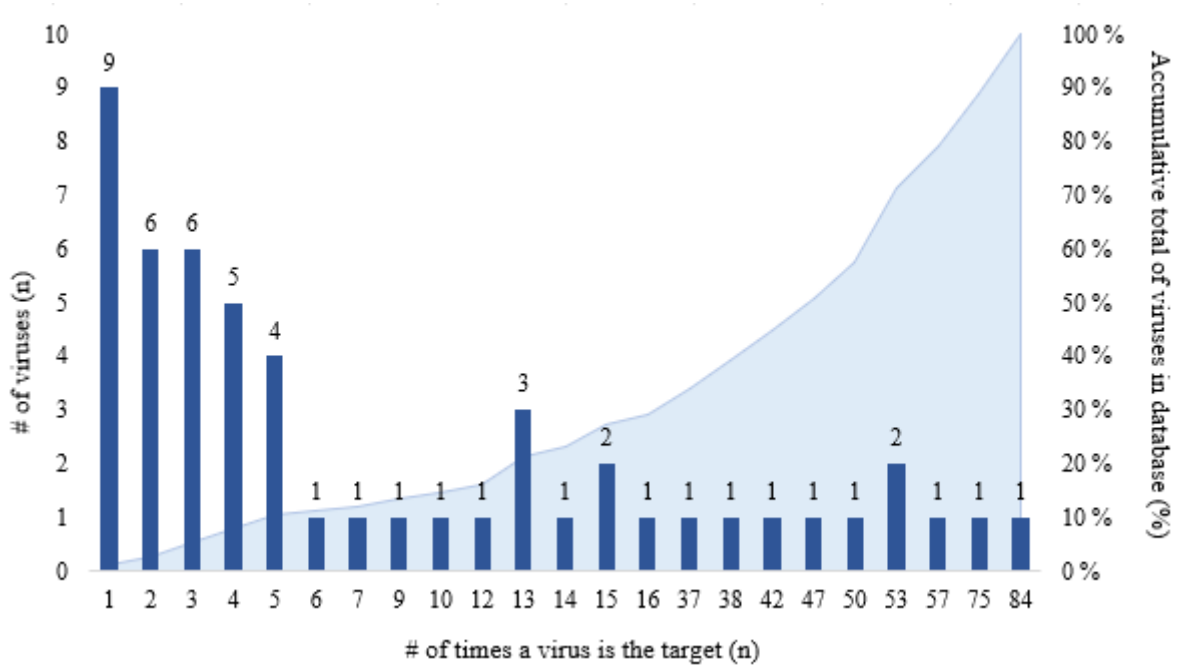

Figure 5: Visual representation of virus frequencies in AVDC. Columns (dark blue) show distribution of viruses based on how often they are the target virus in an entry. Background area (light blue) show accumulative percentage of the viruses in AVDC.

Table 6: Top 10 most frequent viruses in AVDC. These drugs were present in 536 of 758 entries in the database, giving them an inclusion of 70.7 % of all entries.

Virus	# of combinations with target virus in AVDC	% of all AVDC combinations
HCV	84	11.1 %
FLUAV	75	9.9 %
HSV-1	57	7.5 %
CMV	53	7.0 %
HBV	53	7.0 %
EBOV	50	6.6 %
SARS-CoV-2	47	6.2 %
HIV-1	42	5.5 %
HIV	38	5.0 %
HSV-2	37	4.9 %
Total	**536**	**70.7 %**

4.2 Heatmap construction

A two-dimensional heatmap was constructed for easier visualization of the database and the different AVCs tested, and to show their developmental status and target virus variety. All distinct drugs in the finalized AVDC database were identified and sorted alphabetically, and then used as axis for the heatmap. Microsoft Excel was then used to find highest clinical phase entered per AVC, and the number of distinct viruses tested per AVC. The data was then converted from a table to the heatmap using Excel formulas, and basic colour coding was added for easier visualization. The heatmap showed little on its own other than previously tested AVCs and their tested number of viruses, by design, as it is intended to be used with additional databases (Figure 6). The heatmap was too large to be included as a supplementary here, and is instead included as its own external supplementary file.

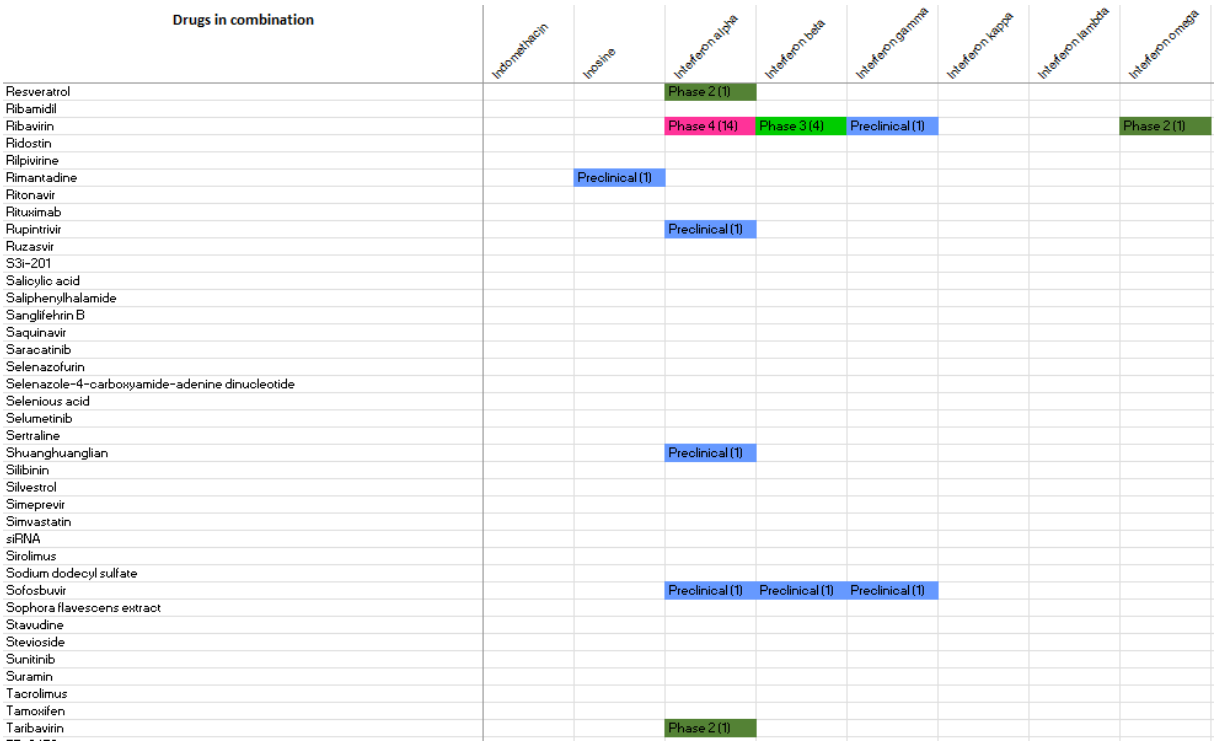

Figure 6: Snapshot of the AVDC database heatmap.

4.3 Using the new AVDC database with the DrugVirus database

4.3.1 Combining AVDC with DrugVirus

The aim for the AVDC database is to provide a foundation for future two-drug AVC discoveries, and to do so its use with additional databases is necessary to identify beneficial and adverse traits for AVCs. Here, the DrugVirus database with information on drug targets, immunomodulatory properties and approval status for 255 BSAs were used together with AVDCs for BCC discoveries and statistical tests.

Only 112 of the 255 BSAs in DrugVirus was also found in the AVDC database, but it covered 302 two-drug AVCs of the 670 distinct AVC and virus target entries in AVDC (Table 7). 270 entries in AVDC included just one BSA. In total, the DrugVirus database covered 22 of the 25 most common drugs identified in AVDC, only missing antibodies, entecavir and ledipasvir (Table 8). Thus, BCC and BSA frequencies were found to be common in AVDC.

Table 7: BSA distribution in combinations from AVDC.

Number of BSAs in combination	Pre-clinical	Phase 0/I	Phase I	Phase II	Phase III	Phase IV	Total	Total % of entries
N = 0	77	5	2	10	2	2	98	14.6 %
N = 1	184	17	8	38	12	11	270	40.3 %
N = 2	233	17	4	20	15	13	302	45.1 %
Total	494	39	14	68	29	26	670	100.0 %

Table 8: Properties of the 25 most frequent drugs in AVDC, with data from DrugVirus. Drugs in italic were not included in DrugVirus.

Drug	Human/viral target	Immuno-modulatory	Approved
Ribavirin	Viral	Yes	Yes
Interferon alpha	Human	No	Yes
Antibodies	*N/A*	*N/A*	*N/A*
Acyclovir	Viral	No	Yes
Oseltamivir	Viral	No	Yes
Interferon beta	Human	No	Yes
Sofosbuvir	Viral	No	Yes
Zidovudine	Viral	Yes	Yes
Favipiravir	Viral	No	Yes
Foscarnet	Viral	No	Yes
Tenofovir	Viral	Yes	Yes
Ganciclovir	Viral	No	Yes
Lamivudine	Viral	No	Yes
Cidofovir	Viral	No	Yes
Interferon gamma	Human	No	No
Ritonavir	Viral	Yes	Yes
vidarabine	Viral	No	Yes
Nitazoxanide	Human	Yes	Yes
Alisporivir	Human	No	No
Artesunate	N/A	Yes	Yes
Daclatasvir	Viral	No	Yes
Entecavir	*N/A*	*N/A*	*N/A*
Ledipasvir	*N/A*	*N/A*	*N/A*
Mycophenolic acid	Human	Yes	Yes
Rupintrivir	Viral	No	No

4.3.2 DrugVirus targets and heatmap

A heatmap to better visualize the drug targets in two-drug AVCs was constructed using the AVDC heatmap and DrugVirus database. The heatmap axis was made using the drug name and targets from the DrugVirus database as axis, and then use the AVDC heatmap as

reference. A requirement for the drug target visualization was therefore that both drugs were BSAs, as DrugVirus was used to assign drug targets, which limited the heatmap to 302 AVCs (Figure 7). Still, it provided valuable clues to AVCs, and it was revealed that 118 out of the 302 combinations in the heatmap had the same target for both drugs. In addition, it was observed that AVCs made of different drugs but with the same targets could have entered different clinical trials. Similarly, it also showed untested AVCs where AVCs of different drugs, but similar targets, showed success. Also using the AVDC heatmap overcome the INDEX/MATCH limitation mentioned earlier and made the process less time consuming and more efficient.

Figure 7: Snapshot of heatmap showing two-drug combinations from the AVDC database, sorted alphabetically by drug targets from the DrugVirus database.

4.3.3 Statistical analysis

Statistical analysis was performed by Pearsons Chi-square of independence, and post hoc adjusted residual analysis.

The number of BSAs in an AVC was not independent and showed a relationship between clinical phase and number of BSAs χ^2 (2, N = 670) = 7.36, p = .025 (Table 9). Residual analysis showed that just one BSA in an AVC had a highly significant advantage of entering clinical phases (z > |2.58|), whereas zero or two BSAs in AVCs had no statistical significance (z < |1.96|). Two BSAs in an AVC had however a confidence level above 90 % (z > |1.64|), showing that two BSAs together could potentially be a disadvantage.

Table 9: Pearsons chi-squared of independence test of BSAs in combinations and their clinical phase, with adjusted residuals analysis. * = α < 0.05 or z > |1.96|, ** = α < 0.01 or z > |2.58|, *** = α < 0.001 or z > |3.29|, † = α < 0.10 or z > 1.64.

		Number of BSAs in combination			
Clinical phase		**n=0**	**n=1**	**n=2**	**Marginals**
Preclinical	Observed	77	184	233	494
	Expected	72.3	199.1	222.7	
	Adj. Res	1.18	-2.70**	1.82†	
Clinical	Observed	21	86	69	176
	Expected	25.7	70.9	79.3	
	Adj. Res	-1.18	2.70**	-1.82†	
Marginals		98	270	302	670
χ^2	7.34				
df	2				
p-value	0.025*				

The DrugVirus database only includes data on BSAs, and both drugs had to therefore be BSAs to look at drug targets. Here I report a significant relationship between the BSAs and human/virus targets χ^2 (2, N = 283) = 8.73, p = .013 (Table 10). Adjusted residuals showed a highly significant negative chance of entering clinical phases when the two BSAs had both

human targets (z > |2.58|). When both BSAs had viral targets, it showed instead a significant positive effect of entering clinical phases (z > |1.96|). An AVC with one human and one viral BSA target showed no advantage or disadvantaged (z < |1.96|).

Table 10: Pearsons chi-squared of independence test of BSA targets in combinations and their clinical phase, with adjusted residuals analysis. * = α < 0.05 or z > |1.96|, ** = α < 0.01 or z > |2.58|, *** = α < 0.001 or z > |3.29|, † = α < 0.10 or z > |1.64|.

		Human/Viral targets of BSAs in combinations			
Clinical stage		**H/H**	**H/V**	**V/V**	**Marginals**
Preclinical	Observed	39	86	92	217
	Expected	32,2	85,1	99,7	
	Adj. Res	2,69**	0,26	-2,17*	
Clinical	Observed	3	25	38	66
	Expected	9,8	25,9	30,3	
	Adj. Res	-2,69**	-0,26	2,17*	
Marginals		42	111	130	283
χ^2	8,73				
df	2				
p-value	0,013*				

The number of BSAs with immunomodulatory properties was also found to be significant on clinical stage, with $\chi^2(2, N = 302) = 7.59$, p = .022 (Table 11). Adjusted residuals showed that AVCs with just one BSA with immunomodulatory properties was highly significantly positive on clinical phase (z > |2.58|), while two non- or immunomodulatory BSAs had no effect (z < |1.96|). AVCs with no immunomodulatory BSAs had confidence levels above 90 % (z > |1.64|) in favour of preclinical stages.

Table 11: Pearsons chi-squared of independence test of immunomodulatory properties to BSAs in combinations, and their clinical phase, with adjusted residuals analysis. * = α < 0.05 or z > |1.96|, ** = α < 0.01 or z > |2.58|, *** = α < 0.001 or z > |3.29|, † = α < 0.10 or z > |1.64|.

		Number of immunomodulatory drugs in BSAs combinations			
Clinical stage		**n=0**	**n=1**	**n=2**	**Marginals**
Preclinical	Observed	88	98	47	233
	Expected	81.8	108.0	43.2	
	Adj. Res	1.79†	-2.75**	1.33	
Clinical	Observed	18	42	9	69
	Expected	24.2	32.0	12.8	
	Adj. Res	-1.79†	2.75**	-1.33	
Marginals		106	140	56	302
χ^2	7.59				
df	2				
p-value	0.022*				

The expected value for no approved drugs at clinical stages fell below the minimum value of 5 when analysing BSA approval status (Table 12). The analysis was thus deemed invalid and inadequate to form any conclusions, but the data hints towards no statistical relationships χ^2 (2, N = 302) = 3.03, p = .22. No adjusted residuals would have been significant, but combinations with one approved BSA was above 90 % confidence level (z > |1.64|).

Table 12: Pearsons chi-squared of independence test of BSAs approval status and in combinations and their clinical phase, with adjusted residuals analysis. * = α < 0.05 or z > 1.96, ** = α < 0.01 or z > 2.58, *** = α < 0.001 or z > 3.29, † = α < 0.10 or z > |1.64|.

		Number of approved drugs in BSAs combinations			
Clinical stage		**n=0**	**n=1**	**n=2**	**Marginals**
Preclinical	Observed	10	87	136	233
	Expected	10.8	81.0	141.2	
	Adj. Res	-0.52	1.72†	-1.46	
Clinical	Observed	4	18	47	69
	Expected	3.2	24.0	41.8	
	Adj. Res	0.52	-1.72†	1.46	
Marginals		14	105	183	302
χ^2	3.03				
df	2				
p-value	0.22				

Finally, it was discovered that 25 of the most frequent antiviral drugs in AVDC had participated in almost half of all drug slots available in the database. It was therefore of interest to determine if those 25 drugs had an advantage over the other 312 drugs in the database. Statistical testing revealed no relationship between the 25 drugs and clinical stage χ^2 (2, N = 670) = 4.31, p = .116 (Table 13). Adjusted residuals also showed no statistical significance (z < |1.96|), although combinations with one of the drugs had a confidence level above 90 % for positive effect on clinical stage (z > |1.64|), and confidence level above 90 % for negative effect on clinical stage with two of the drugs in combinations (z > |1.64|).

Table 13: Pearsons chi-squared of independence test of the 25 most frequent drugs by drug slots in combinations, with adjusted residuals analysis. * = α < 0.05 or z > 1.96, ** = α < 0.01 or z > 2.58, *** = α < 0.001 or z > 3.29, † = α < 0.10 or z > |1.64|.

	Number of top 25 most frequent

		drugs in combinations			
Clinical stage		**n=0**	**n=1**	**n=2**	**Marginals**
Preclinical	Observed	145	224	125	494
	Expected	141.6	235.2	83.8	
	Adj. Res	0.61	-1.84†	1.89†	
Clinical	Observed	47	95	34	176
	Expected	50.4	83.8	41.8	
	Adj. Res	-0.61	1.84†	-1.89†	
Marginals		192	319	159	670
χ^2	4.31				
df	2				
p-value	0.116				

4.4 Updating DrugVirus with BCCs, and model predictions

4.4.1 Updating DrugVirus with BCCs

The use of AVDC and the BSA data from DrugVirus made it possible to find and extract BCCs in AVDC with at least one BSA. 407 BCCs was added to the DrugVirus database, as part of a major update to the DrugVirus database by my research group (37). The BCCs was included with additional corresponding data if applicable, such as clinical stages, cell- or animal models, and drug targets. The update also featured additional BSAs to the DrugVirus database.

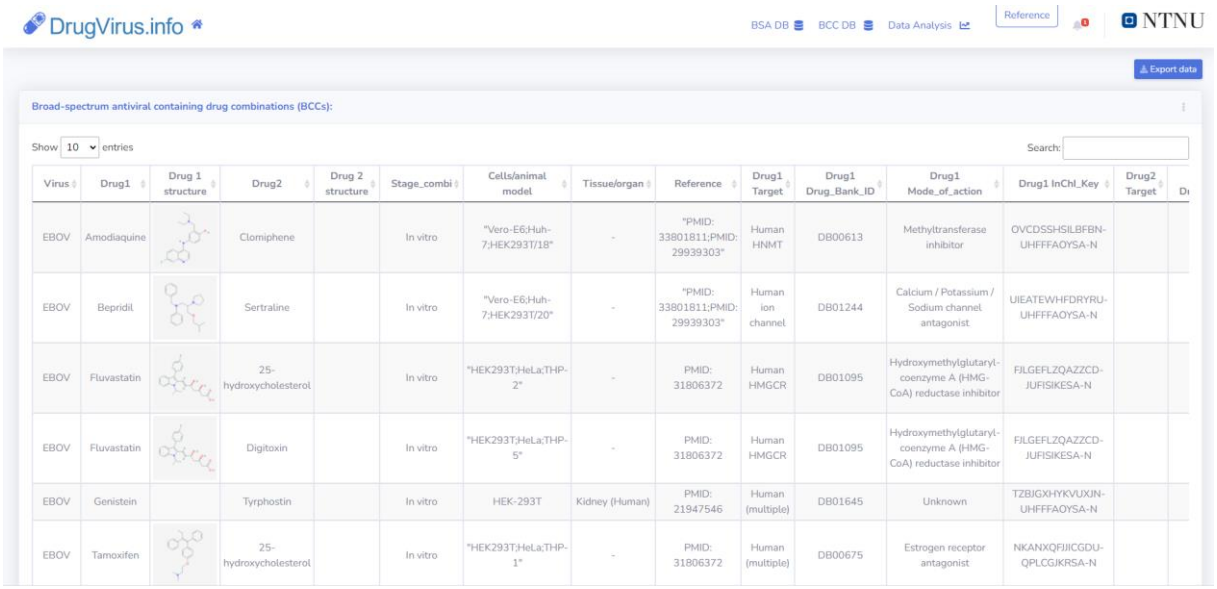

Figure 8: Snapshot of the new edition of DrugVirus.info, now with added BCCs.

4.4.2 Model predictions

Using a model based on first individual drug scoring followed by two-drug combinational scoring, resulted in 87 predicted BCCs, 12 of which already being included in the AVDC database (Table 14). AVDC thus showed its potential as a reference for model predictions, although the predicted BCCs needs to be confirmed *in vitro*.

Table 14: Predicted BCCs based on our model described in detail in a separate paper, with AVDC used as a reference (38). Copied with permission.

Virus	Family	Case fat. rate, %	Infected system	Drug 1 Drug 2	Sum of BSA scores	BCC score	Reference
				Published BCCs			
EBOV	*Filoviridae*	66	Multiple	Favipiravir Merimepodib	10.0	15.8	(Tong *et al.*, 2018)
LASV	*Arenaviridae*	13	Multiple	Ribavirin Merimepodib	9.0	14.3	(Tong *et al.*, 2018)
HIV-1	*Retroviridae*	47	Multiple	Amprenavir Efavirenz	12	17.3	(Falloon et al., 2000)
				Efavirenz Indinavir	12	17.3	NCT00002387
FLUAV	*Orthomyxoviridae*	0.003	Respiratory system	Favipiravir Pimodivir	11.8	16.9	(Byrn et al., 2015)
				IFN-a Ribavirin	9.5	15.1	NCT01146535

HBV	*Hepadnaviridae*	40	Multiple	Telbivudine Alisporivir	9.3	14.7	(Phillips et al., 2015)
HCV	*Flaviviridae*	6.3	Multiple	Daclatasvir Sofosbuvir	12	17.3	NCT03200184
				Daclatasvir Simeprevir	12	17.3	NCT01628692
				Mericitabine IFN-a	10.8	17.0	(Wedemeyer et al., 2013)
				Ribavirin IFN-a	10	15.8	(Bellobuono et al., 1997)
ZIKV	*Flaviviridae*	n.a.	Multiple	Favipiravir IFN-a	9.5	15.05	(Pires de Mello et al., 2018)

5 Discussion

The development and prediction of AVCs for emerging and re-emerging viruses would reduce the severity of the next pandemic, but identifying beneficial traits of AVCs and the development of mathematical or *in silico* models are first needed. The AntiviralCombi database was the first database to centralize date on tested AVCs in clinical and preclinical trials, and provided an excellent starting point for additional work. Its initial 985 entries meant that considerable time had already being invested in literature searches, and resources could instead be put towards refinement and analysis. Refinement started here with antiviral drug name, virus name, and clinical phase standardization, with the focus being on just two-drug AVCs. These refinements decreased the number of entries from originally 985 entries to 708, a 31 % reduction. Additional literature searches increased the final number of entries in AVDC to 758, split into 670 distinct and 88 non-distinct combination and virus entries. Just true duplicates who shared all entry fields were removed from AVDC, although entries sharing drug combination and viruses, but different clinical phases or models (e.g. cell cultures, animal model) was kept, as previously it has been shown that models can have an impact on preclinical tests (43). However, the initial 31 % reduction during refinement was primarily due to the focus being on two-drug AVCs and not due to removal of duplicate entries. While this focus might have reduced the overall complexity of different variables for *in vitro* and statistical testing, it is also an advantage in many cases as increased number of drugs may increase toxicity (34). The two-drug AVC approach might be advantageous in

earlier stages, but a revisit of AntiviralCombi might be needed later when our knowledge of two-drug AVCs is established and more complex AVCs are to be investigated.

The literature searches were conducted using several search engines and databases, which expanded AVDC to its total of 758 entries. During the searches it was seen that most of the new entries were not from articles published after the release of the AntiviralCombi database, which was taken as an indication that the searches found additional articles not uncovered while building AntiviralCombi. Indeed, the AntiviralCombi database focused primarily on using non-specific queries such as “combination”, “combination therapy”, while my searches also included the two antiviral drugs by their specific names. By including more quires in my searches, I also got a broader coverage of the databases used in the searches, and thus more precise search results. Another potential finding is that my literature searches went through thousands of articles only to return 50 additional entries, which may suggest that AVDC has a good coverage of currently tested two-drug AVCs. But although the searches found additional drug combinations not included in AntiviralCombi, it is possible that a more refined searching method could uncover additional entries for the AVDC database. The literature searches performed here were done manually by one person, and additional personnel and/or automatic literature searches in additional databases could increase or update entries even further. Another limitation in my searches were the focus on drugs and ignoring viruses, which may explain why some viruses are more dominating than others. Avoiding these limitations should be a focus points if AVDC receive an update in the future.

One potential bias for AVDC is the frequency that some antiviral drugs and viruses are included. With the 25 most frequent antiviral drugs participating in nearly 50 % of all drug slots in the database, and with the 10 most frequent viruses included in 70 % of all entries, this could influence statistical tests and models if constructed. A solution to this potential problem is to perform more complex statistical tests focused on specific drugs and viruses, but another option would also be to perform additional literature searches on under-represented AVCs and viruses in the database. Some antivirals could occur more frequent simply by the fact that some antivirals are more popular than others. If an antiviral is approved for instance, it could be tested for repurposing with additional pathogens to save time and costs, with these tests ending up in AVDC. The most frequent drugs in AVDC were also common drugs in mono-drug treatments for the most frequent viruses in AVDC (13). Some viruses may also simply be more frequently tested on if no other treatment option rather than antivirals drugs is

available, and therefore may have more research put into them. Such is the case with HCV, and previous studies on mono-drug treatments seems to also make this suggestion (37, 48).

Using AVDC together with other databases was a focus point when creating the database, as additional data are needed with AVDC to identify beneficial traits. Its standardization was therefore important, and by sorting the two antiviral drugs alphabetically, additional data can be easily added or substituted by the user. Such data can be the addition of drug traits, as used in this thesis, but also if changes occur to the drug or virus name. Excel formulas such as INDEX and MATCH can be used in these cases, but also more complex tools if needed. Also, by having all entries standardized, more focus can be put into expanding supplementary databases as seen with the addition of BCCs to the DrugVirus database. Here the DrugVirus database was used with the AVDC database, both for analysing AVDC with the help of DrugVirus, but also to demonstrate the potential of AVDC to reveal beneficial or adverse traits for AVC success. The coverage of DrugVirus in the AVDC database was initially seen as suboptimal with only 112 of the 255 BSAs from DrugVirus being present in AVDC, but the actual coverage of DrugVirus was decent with 270 and 302 of the 670 entries including one or two BSAs in their AVCs, respectively. With the number of BSA including AVCs being 572 entries, it also shows how often BCCs are used as basis for AVCs.

A BSA drug-target heatmap was constructed by using the AVDC heatmap, which was both an easier method and also required less processing time than during the original AVDC heatmap construction. The heatmap showed that 118 out of the 302 AVCs included in the heatmap had the same antiviral target. It was also seen that two or more antivirals with the same target could have entered different clinical stages, even when they were combined with the same second antiviral. For instance, the drugs lopinavir, indinavir and darunavir all targets viral protease, but their individual combination with ritonavir had entered clinical phase IV, phase II, and phase III respectively, and tested on four, one and one viruses respectively. The observed differences among antivirals with similar targets in the heatmap could have many origins, but the simplest explanation could be that a given drug has not been tested as frequent as the others. Antiviral interference could very well also be a factor, as DrugVirus uses broad terms for drug targets that may be narrowed down even further, which could have been an advantage here. Lastly one drug may also have several targets, and it is possible that some specific antiviral targets interfere more with each other than others. My statistical testing

included human and virus targets, but more precise terms for antiviral targets and statistical testing on specific BSA targets could revealed traits not here discovered.

Statistical testing was used to look deeper into drug traits for future combinations, even though some antivirals and viruses were more frequent in the database than others. Here, a chi-square of independence with adjusted residual analysis was used to identify traits of interest.

The number of BSAs in AVCs was not found be independent, with combinations including just one BSA being advantageous compared to AVCs with none or two BSAs. AVCs with two BSAs showed additionally potential to be a negative trait, but why AVCs with one BSAs showed such a difference compared to none or two BSAs remained elusive.

Human/viral targets for AVCs was not independent and showed a highly significant negative effect on clinical stage when two antivirals with human targets were combined. Antivirals with human targets will often have a toxic effect when combined, and by combining two such antivirals they could interact antagonistically (38). This would explain why there were only three AVCs found in AVDC with two human targets and who had entered clinical trials. Adjusted residuals for AVCs with a human and a viral target showed a neutral effect on clinical phase, but a two viral target combination had a significant positive effect.
Thus, the statistical test suggests that the more drugs with viral targets in an AVC, the higher the chance is that it has entered clinical trials, as also seen previously (33)

Immunomodulatory properties and clinical phases were not independent, and adjusted residual analysis showed a highly significant advantage when one of the two drugs were immunomodulatory. Two immunomodulatory drugs did not show to affect clinical phase, while no immunomodulatory drugs showed to potentially be a disadvantage. Immunomodulatory drugs can both be beneficial and have adverse effects, and it is possible that when two immunomodulatory effects are combined it creates antagonistic synergy. However, the specific way an immunomodulatory drug functions were not included in DrugVirus and made it difficult to identify specifics.

Approval status for the BSAs was possibly independent for individual drug approval, but the statistical approach used here was inadequate to form any conclusions based on the current

data. Adjusted residual analysis might have showed a disadvantage for combinations using only one approved BSA in combinations, but with an expected value below the five-value threshold for the chi-square of independence, it suggests very little. Although for approval status as an antiviral trait, the focus should not necessary be primarily on its effect in AVCs, but rather on the time and cost savings with drug repurposing when faced with new pathogenic viruses.

The 25 most frequent drugs by drug slots were included in the statistical tests after their high drug slot participation was discovered, as to investigate their effectiveness. When the DrugVirus database was coupled with AVDC it was seen that antibodies, entecavir and ledipasvir was the only three drugs out of the 25 to not be included in the DrugVirus database, and out of the remaining 22 all but interferon gamma and alisporivir was approved (the latter two being in clinical trials). Considering their high drug slot participation in the database it was therefore of interest to investigate if these drugs had an advantage in combinations compared to the remaining 312 drugs. The statistical test indicated no significance on the use of the 25 most frequent drugs and their effect on clinical stage. However, adjusted residual analysis showed that the use of one of the 25 drugs in AVCs could potentially be beneficial, and the use of two should possibly be avoided. These residuals follow the same pattern as the residuals of the test of BSAs in combinations, and with 22 out of the 25 most frequent drugs also being BSAs, some overlap between these tests could have occurred.

While these tests showed some factors that can be of interest to future combinations, it did not include statistical analysis with multiple traits. The tests with drug target, immunomodulatory properties and approval status were somewhat multiple tests as they were also BSAs, but multi-level testing of the traits available was not performed due to the primary focus of this thesis being on database construction. As previously mentioned, the testing was performed using all distinct AVCs which may affect the tests due to the frequency of some antivirals and viruses. Future statistical tests could be performed for individual or sub-groups of antivirals and viruses as an alternative. The tests however gave valuable clues as to what traits could be beneficial to AVC, and future *in vitro* tests should be performed to investigate these findings further.

Lastly, the AVDC database demonstrated its potential to expand existing databases with the introduction of BCCs to the DrugVirus database. It was also used as a reference with the

results of our BCC predictions. With the majority of AVCs in AVDC also being BCCs, both AVDC and DrugVirus could benefit from deeper dives into individual drug traits. Ultimately the end goal should be making predictions accurately and quickly, which would be needed for combating future viral threats.

6 Conclusion

New drugs and methods are needed for combating emerging and re-emerging viral threats, and combination therapy and drug repurposing show the potential to fill such a role. Here the AVC database AntiviralCombi was standardized and converted to a two-drug AVC database AntiviralDualCombi, and expanded by additional literature searches. BSAs targets several different viral families, and their inclusion in AVCs as BCCs would be beneficial for drug discoveries. The DrugVirus database was used together with AVDC to investigate beneficial and adverse traits of AVCs and BCCs by heatmaps and statistical tests, and it revealed possible traits that needs *in vitro* validation. Future statistical analysis with narrower data categories can possibly pinpoint traits even further. It also uncovered previously tested BCCs that were included in a new version of DrugVirus. A mathematical model for BCC predictions were also constructed by our research group, and together with the statistical tests it shows promising results for future *in vitro* testing. Additional databases could also be used together with AVDC for additional analysis and AVC/BCC predictions, and more efficient literature searches would also be beneficial.

References

1. Talic S, Shah S, Wild H, Gasevic D, Maharaj A, Ademi Z, et al. Effectiveness of public health measures in reducing the incidence of covid-19, SARS-CoV-2 transmission, and covid-19 mortality: systematic review and meta-analysis. BMJ. 2021;375:e068302.
2. Kang M, Song T, Zhong H, Hou J, Wang J, Li J, et al. Contact Tracing for Imported Case of Middle East Respiratory Syndrome, China, 2015. Emerg Infect Dis. 2016;22(9):1644-6.
3. Swanson KC, Altare C, Wesseh CS, Nyenswah T, Ahmed T, Eyal N, et al. Contact tracing performance during the Ebola epidemic in Liberia, 2014-2015. PLOS Neglected Tropical Diseases. 2018;12(9):e0006762.
4. Dolgin E. The race for antiviral drugs to beat COVID - and the next pandemic. Nature. 2021;592(7854):340-3.
5. Woolhouse MEJ, Gowtage-Sequeria S. Host range and emerging and reemerging pathogens. Emerg Infect Dis. 2005;11(12):1842-7.
6. Woolhouse MEJ, Haydon DT, Antia R. Emerging pathogens: the epidemiology and evolution of species jumps. Trends in Ecology & Evolution. 2005;20(5):238-44.
7. Harrington WN, Kackos CM, Webby RJ. The evolution and future of influenza pandemic preparedness. Experimental & molecular medicine. 2021;53(5):737-49.
8. Howard CR, Fletcher NF. Emerging virus diseases: can we ever expect the unexpected? Emerging Microbes & Infections. 2012;1(1):1-9.
9. Webster RG, Govorkova EA. Continuing challenges in influenza. Annals of the New York Academy of Sciences. 2014;1323(1):115-39.
10. Monto A. Vaccines and Antiviral Drugs in Pandemic Preparedness. Emerging Infectious Disease journal. 2006;12(1):55.
11. Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. Cochrane database of systematic reviews. 2014(4).
12. Herrman EC, Jr. Plaque inhibition test for detection of specific inhibitors of DNA containing viruses. Proc Soc Exp Biol Med. 1961;107:142-5.
13. Clercq ED, Li G. Approved Antiviral Drugs over the Past 50 Years. Clinical Microbiology Reviews. 2016;29(3):695-747.
14. Andersen PI, Ianevski A, Lysvand H, Vitkauskiene A, Oksenych V, Bjørås M, et al. Discovery and development of safe-in-man broad-spectrum antiviral agents. International Journal of Infectious Diseases. 2020;93:268-76.
15. Öberg B. Antiviral effects of phosphonoformate (pfa, foscarnet sodium). Pharmacology & Therapeutics. 1989;40(2):213-85.
16. Choi YK. Emerging and re-emerging fatal viral diseases. Experimental & Molecular Medicine. 2021;53(5):711-2.
17. Ianevski A, Andersen PI, Merits A, Bjørås M, Kainov D. Expanding the activity spectrum of antiviral agents. Drug Discovery Today. 2019;24(5):1224-8.
18. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Final Report. New England Journal of Medicine. 2020;383(19):1813-26.
19. Debing Y, Neyts J, Delang L. The future of antivirals: broad-spectrum inhibitors. Current Opinion in Infectious Diseases. 2015;28(6):596-602.
20. D'Elia RV, Harrison K, Oyston PC, Lukaszewski RA, Clark GC. Targeting the “Cytokine Storm” for Therapeutic Benefit. Clinical and Vaccine Immunology. 2013;20(3):319-27.

21. Fajgenbaum DC, June CH. Cytokine Storm. New England Journal of Medicine. 2020;383(23):2255-73.
22. Nosengo N. Can you teach old drugs new tricks? Nature. 2016;534(7607):314-6.
23. Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. Biostatistics. 2018;20(2):273-86.
24. Prusoff WH. Synthesis and biological activities of iododeoxyuridine, an analog of thymidine. Biochim Biophys Acta. 1959;32(1):295-6.
25. Hernandez JJ, Pryszlak M, Smith L, Yanchus C, Kurji N, Shahani VM, et al. Giving Drugs a Second Chance: Overcoming Regulatory and Financial Hurdles in Repurposing Approved Drugs As Cancer Therapeutics. Frontiers in Oncology. 2017;7.
26. Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nature Reviews Drug Discovery. 2004;3(8):673-83.
27. Pizzorno A, Padey B, Terrier O, Rosa-Calatrava M. Drug Repurposing Approaches for the Treatment of Influenza Viral Infection: Reviving Old Drugs to Fight Against a Long-Lived Enemy. Frontiers in Immunology. 2019;10.
28. Bekerman E, Einav S. Combating emerging viral threats. Science. 2015;348(6232):282-3.
29. Jilek BL, Zarr M, Sampah ME, Rabi SA, Bullen CK, Lai J, et al. A quantitative basis for antiretroviral therapy for HIV-1 infection. Nature Medicine. 2012;18(3):446-51.
30. Bourlière M, Pietri O. Hepatitis C virus therapy: No one will be left behind. International Journal of Antimicrobial Agents. 2019;53(6):755-60.
31. White JM, Schiffer JT, Ignacio RAB, Xu S, Kainov D, Ianevski A, et al. Drug Combinations as a First Line of Defense against Coronaviruses and Other Emerging Viruses. mBio. 2021;12(6):e03347-21.
32. Zoulim F. Combination of nucleoside analogues in the treatment of chronic hepatitis B virus infection: lesson from experimental models. Journal of Antimicrobial Chemotherapy. 2005;55(5):608-11.
33. Ianevski A, Yao R, Biza S, Zusinaite E, Mannik A, Kivi G, et al. Identification and Tracking of Antiviral Drug Combinations. Viruses. 2020;12(10):1178.
34. Radhakrishnan ML, Tidor B. Optimal Drug Cocktail Design: Methods for Targeting Molecular Ensembles and Insights from Theoretical Model Systems. Journal of Chemical Information and Modeling. 2008;48(5):1055-73.
35. Ianevski A, Zusinaite E, Kuivanen S, Strand M, Lysvand H, Teppor M, et al. Novel activities of safe-in-human broad-spectrum antiviral agents. Antiviral Research. 2018;154:174-82.
36. Andersen PI, Krpina K, Ianevski A, Shtaida N, Jo E, Yang J, et al. Novel Antiviral Activities of Obatoclax, Emetine, Niclosamide, Brequinar, and Homoharringtonine. Viruses. 2019;11(10):964.
37. Ianevski A, Simonsen RM, Myhre V, Tenson T, Oksenych V, Bjørås M, et al. DrugVirus.info 2.0: an integrative data portal for broad-spectrum antivirals (BSA) and BSA-containing drug combinations (BCCs). Nucleic Acids Research. 2022 (In press).
38. Ianevski A, Yao R, Simonsen RM, Myhre V, Ravlo E, Kaynova GD, et al. Mono- and combinational drug therapies for global viral pandemic preparedness. iScience. 2022;25(4):104112.
39. Nagaraj AB, Wang QQ, Joseph P, Zheng C, Chen Y, Kovalenko O, et al. Using a novel computational drug-repositioning approach (DrugPredict) to rapidly identify potent drug candidates for cancer treatment. Oncogene. 2018;37(3):403-14.
40. AntiviralCombi database [Internet]. NTNU Medical System Virology Research Group. 2021 [cited 11.08.2021]. Available from: AntiviralCombi.info

41. Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, et al. DrugBank 5.0: a major update to the DrugBank database for 2018. Nucleic Acids Res. 2018;46(D1):D1074-d82.
42. DrugVirus.info [Internet]. NTNU Medical System Virology Research Group. 2021 [cited 16.01.2022]. Available from: DrugVirus.info.
43. Dittmar M, Lee JS, Whig K, Segrist E, Li M, Kamalia B, et al. Drug repurposing screens reveal cell-type-specific entry pathways and FDA-approved drugs active against SARS-Cov-2. Cell Reports. 2021;35(1):108959.
44. Sharpe D. Chi-square test is statistically significant: Now what? Practical Assessment, Research, and Evaluation. 2015;20(1):8.
45. Agresti A. An introduction to categorical data analysis: John Wiley & Sons; 2018.
46. Lefkowitz EJ, Dempsey DM, Hendrickson RC, Orton RJ, Siddell SG, Smith DB. Virus taxonomy: the database of the International Committee on Taxonomy of Viruses (ICTV). Nucleic Acids Research. 2017;46(D1):D708-D17.
47. Walker PJ, Siddell SG, Lefkowitz EJ, Mushegian AR, Adriaenssens EM, Dempsey DM, et al. Changes to virus taxonomy and the Statutes ratified by the International Committee on Taxonomy of Viruses (2020). Archives of Virology. 2020;165(11):2737-48.
48. Chaudhuri S, Symons JA, Deval J. Innovation and trends in the development and approval of antiviral medicines: 1987–2017 and beyond. Antiviral Research. 2018;155:76-88.

Supplementary

Supplementary included here are Microsoft Excel formulas used during the thesis, an expanded table of the 25 most frequent drugs, and a copy of AVDC. An additional supplementary file included a copy of AVDC, the AVDC heatmap, the drug target heatmap, and a copy of DrugVirus and AntiviralCombi used for the thesis.

S1 Excel formulas

I used multiple Microsoft Excel formulas throughout my thesis, formulas that may not be familiar to the reader. All individual formulas are therefore listed here, although limited to simple formulas and not formulas-within-formulas (Supplementary Table A).

Supplementary Table A: Excel formula descriptions and their syntaxes. Each formula and its arguments are described in detail, including arguments that are optional (in brackets).

Formula and syntax	Formula description
COUNTIF(array, criteria)	Counts number of cells that meets the set criteria in an array.
FILTER(array,include, [if empty])	Returns the original array filtered for a single or multiple criteria. If multiple criteria are used, "include" should have a single array and a signel criteria added in closed paranthesis, joing together by an asterisk (e.g. (A1:A5="Virus")*(B1:B5="Drug")). It is also possible to include what FILTER should return no entries in the array include the set criteria.
IF(logical text, [if true], [if false])	Returns a set value based on if the logical argument is true or false.
IFERROR(value, value if error)	If the value (i.e. a formula) returns no errors the value (i.e. the formula) will be used. If the value returns an error the alternative value if error will be used instead.
INDEX(array, MATCH(),MATCH())	Combines INDEX and MATCH. Retrieves specific values from a given array, that correspond to a position given by MATCH.
INDEX(array, row_num, [column_num])	Returns the value in an array at a specific coordinate, determined by row number and optional column number if the array includes multiple columns.
MATCH(lookup value, lookup array, [match type])	Returns the position of a value in an one-dimensional array (i.e. either one column and multiple rows, or one rows with multiple columns). Match type can be less-or-equal (-1), equal (0), or greater-or-equal (1) to target value. Match type is set to 1 by default if not specified. A limitation with MATCH is that it does not check if multiple values matches the criteria, so it always returns the position of the first matching value in the array and ignores other.
MAXIFS(max range, criteria range 1, criteria 1, [criteria range 2, criteria 2]…)	Returns the maximal value of an array by one or multiple criteria and criteria ranges.
ROWS(array)	Counts number of rows in an array
SORT(array,[sort index],[sort order], [by column])	Sorts an array. Sort index can be set to specify which column to sort by, default set to 1. Sort order can be set to default ascending (1) or descending (2). By column specifies if it is by column (default, TRUE or 1) or row (FALSE or 0).

S2 Expanded 25 drug table

During the analysis of the AVDC database it was discovered that the 25 most frequent drugs by drug slots was included in nearly half of all drug slots. Additional analyses were thus performed to see if they had advantages over other drugs, including individual drug participation for each clinical phase (Supplementary Table B).

Supplementary Table B: Break down of drug participation in clinical stages for the 25 highest drug slot participants. # are drug slots for each drug in a clinical phase. % are the percentage of # in relation to all drug slots for the given clinical phase.

Drug		Pre-clinical	Phase 0/1	Phase I	Phase II	Phase III	Phase IV	Total
Ribavirin	#	76	13	2	11	4	4	110
	%	7.0 %	14.4 %	7.1 %	6.8 %	4.7 %	6.7 %	7.3 %
Interferon alpha	#	50	11	1	14	3	8	87
	%	4.6 %	12.2 %	3.6 %	8.6 %	3.5 %	13.3 %	5.7 %
Antibodies	#	44	5	0	0	1	0	50
	%	4.0 %	5.6 %	0.0 %	0.0 %	1.2 %	0.0 %	3.3 %
Acyclovir	#	44	1	0	0	0	0	45
	%	4.0 %	1.1 %	0.0 %	0.0 %	0.0 %	0.0 %	3.0 %
Oseltamivir	#	30	0	0	6	4	0	40
	%	2.8 %	0.0 %	0.0 %	3.7 %	4.7 %	0.0 %	2.6 %
Interferon beta	#	29	0	0	0	2	0	31
	%	2.7 %	0.0 %	0.0 %	0.0 %	2.3 %	0.0 %	2.0 %
Sofosbuvir	#	15	0	0	5	6	5	31
	%	1.4 %	0.0 %	0.0 %	3.1 %	7.0 %	8.3 %	2.0 %
Zidovudine	#	13	2	4	8	4	0	31
	%	1.2 %	2.2 %	14.3 %	4.9 %	4.7 %	0.0 %	2.0 %
Favipiravir	#	27	1	0	1	0	1	30
	%	2.5 %	1.1 %	0.0 %	0.6 %	0.0 %	1.7 %	2.0 %
Foscarnet	#	26	3	0	0	1	0	30
	%	2.4 %	3.3 %	0.0 %	0.0 %	1.2 %	0.0 %	2.0 %
Tenofovir	#	14	0	1	7	4	4	30
	%	1.3 %	0.0 %	3.6 %	4.3 %	4.7 %	6.7 %	2.0 %
Ganciclovir	#	23	1	0	2	1	0	27
	%	2.1 %	1.1 %	0.0 %	1.2 %	1.2 %	0.0 %	1.8 %

Lamivudine	#	10	1	0	4	5	5	25
	%	0.9 %	1.1 %	0.0 %	2.5 %	5.8 %	8.3 %	1.6 %
Cidofovir	#	23	1	0	0	0	0	24
	%	2.1 %	1.1 %	0.0 %	0.0 %	0.0 %	0.0 %	1.6 %
Interferon gamma	#	23	0	0	0	0	0	23
	%	2.1 %	0.0 %	0.0 %	0.0 %	0.0 %	0.0 %	1.5 %
Ritonavir	#	3	5	0	6	5	4	23
	%	0.3 %	5.6 %	0.0 %	3.7 %	5.8 %	6.7 %	1.5 %
vidarabine	#	19	0	0	0	0	0	19
	%	1.7 %	0.0 %	0.0 %	0.0 %	0.0 %	0.0 %	1.3 %
Nitazoxanide	#	10	0	0	1	2	0	13
	%	0.9 %	0.0 %	0.0 %	0.6 %	2.3 %	0.0 %	0.9 %
Alisporivir	#	8	1	0	3	0	0	12
	%	0.7 %	1.1 %	0.0 %	1.9 %	0.0 %	0.0 %	0.8 %
Artesunate	#	11	1	0	0	0	0	12
	%	1.0 %	1.1 %	0.0 %	0.0 %	0.0 %	0.0 %	0.8 %
Daclatasvir	#	7	0	0	3	1	1	12
	%	0.6 %	0.0 %	0.0 %	1.9 %	1.2 %	1.7 %	0.8 %
Entecavir	#	2	0	1	3	1	5	12
	%	0.2 %	0.0 %	3.6 %	1.9 %	1.2 %	8.3 %	0.8 %
Ledipasvir	#	6	0	0	2	3	1	12
	%	0.6 %	0.0 %	0.0 %	1.2 %	3.5 %	1.7 %	0.8 %
Mycophenolic acid	#	11	0	0	0	0	1	12
	%	1.0 %	0.0 %	0.0 %	0.0 %	0.0 %	1.7 %	0.8 %
Rupintrivir	#	12	0	0	0	0	0	12
	%	1.1 %	0.0 %	0.0 %	0.0 %	0.0 %	0.0 %	0.8 %
Total #		**536**	**46**	**9**	**76**	**47**	**39**	**753**
Total %		**49.2 %**	**51.1 %**	**32.1 %**	**46.9 %**	**54.7 %**	**65.0 %**	**49.7 %**
AVCD total #		**1090**	**90**	**28**	**162**	**86**	**60**	**1516**

S3 AntiviralDualCombi database

The entire AVDC database is here copied to provide an easy way of copying it into other data-managing tools, for future use (Supplementary Table C).

Supplementary Table C: The AntiviralDualCombi database.

Reference	Clinical phase	Cell line/animal model	Drug1	Drug2	Virus
PMID: 16340198	Preclinical	Vero	(22S,23S)-3beta-bromo-5alpha,22,23-trihydroxystigmastan-6-one	Foscarnet	HSV-1
PMID: 22496216	Preclinical	HeLa	(23,25)trans-epoxysuccinyl-l-leucylamindo-3-methylbutane ethyl ester (EST)	Camostat	SARS-CoV
PMID: 22738253	Preclinical	Porcine Stable kidney	(MIBT) derivative (SCH16)	Mycophenolic acid	JEV
PMID: 22738253	Preclinical	Porcine Stable kidney	(MIBT) derivative (SCH16)	Pentoxifylline	JEV
PMID: 22738253	Preclinical	Porcine Stable kidney	(MIBT) derivative (SCH16)	Ribavirin	JEV
PMID: 15026197	Preclinical	Cell cultures	2-alpha-hydroxybenzyl-benzimidazole (HBB)	Arildone	CVB-1
PMID: 15026197	Preclinical	Cell cultures	2-alpha-hydroxybenzyl-benzimidazole	Disoxaril	CVB-1

			(HBB)		
PMID: 15026197	Preclinical	Cell cultures	2-alpha-hydroxybenzyl-benzimidazole (HBB)	Ethyl 4-methyl-2-(methylthio)pyrimidine-5-carboxylate	CVB-1
PMID: 10757231	Preclinical	FL cells	2-alpha-hydroxybenzyl-benzimidazole (HBB)	Guanidine	PV
PMID: 10757231	Preclinical	FL cells	2-alpha-hydroxybenzyl-benzimidazole (HBB)	Arildone	PV
PMID: 10757231	Preclinical	FL cells	2-alpha-hydroxybenzyl-benzimidazole (HBB)	Disoxaril	PV
PMID: 10757231	Preclinical	FL cells	2-alpha-hydroxybenzyl-benzimidazole (HBB)	Ethyl 4-methyl-2-(methylthio)pyrimidine-5-carboxylate	PV
PMID: 1271013	Preclinical	Mice	2-alpha-hydroxybenzyl-benzimidazole (HBB)	Guanidine	HEV-B
PMID: 1271013	Preclinical	Mice	2-alpha-hydroxybenzyl-benzimidazole (HBB)	Guanidine	HRV-A9

PMID: 6299189	Preclinical	Mice	2-alpha-hydroxybenzyl-benzimidazole (HBB)	Guanidine	HRV-A9
PMID: 30153445	Preclinical	HFF	2-bromo-5,6-dichloro-1-beta-D-riborfuranosyl benzimidazole riboside (BDCRB)	Brincidofovir	CMV
PMID: 30153445	Preclinical	HFF	2-bromo-5,6-dichloro-1-beta-D-riborfuranosyl benzimidazole riboside (BDCRB)	Cidofovir	CMV
PMID: 30153445	Preclinical	HFF	2-bromo-5,6-dichloro-1-beta-D-riborfuranosyl benzimidazole riboside (BDCRB)	Cyclopropavir	CMV
PMID: 30153445	Preclinical	HFF	2-bromo-5,6-dichloro-1-beta-D-riborfuranosyl benzimidazole riboside (BDCRB)	Ganciclovir	CMV
PMID: 24890597	Preclinical	HG23	2'-C-methylcytidine	Rupintrivir	NoV

PMID: 26036224	Preclinical	Huh 9-13; HuH6; Huh 5-2 cells	2'-C-methylcytidine	Tegobuvir	HCV
PMID: 27035622	Preclinical	Huh7	2'-C-methylcytidine	Sofosbuvir	HCV
PMID: 27035622	Preclinical	Huh7.5.1; Con1b cells	2'-C-Methylcytidine	Chlorcyclizine	HCV
PMID: 31362004	Preclinical	PLC/PRF/5	2'-C-methylcytidine	Ribavirin	HEV
PMID: 31362004	Preclinical	PLC/PRF/5	2'-C-methylguanine	Interferon alpha	HEV
PMID: 31362004	Preclinical	PLC/PRF/5	2'-C-methylguanine	Interferon beta	HEV
PMID: 31362004	Preclinical	PLC/PRF/5	2'-C-methylguanine	Interferon gamma	HEV
PMID: 31362004	Preclinical	PLC/PRF/5	2'-C-methylguanine	Ribavirin	HEV
PMID: 3777913	Preclinical	Mice	2'-fluoro-5-iodoaracytosine (FIAC)	vidarabine	HSV-2
PMID: 3777913	Preclinical	Mice	2'-fluoro-5-methylarauracil (FMAU)	vidarabine	HSV-2
PMID: 6299189	Preclinical	Mice	2-guanidino-benzimidazole (GB)	Guanidine	HRV-A9

PMID: 20054446	Preclinical	Mice	2-Phenylamino-6-oxo-9-(4-hydroxybutyl) purine (HBPG)	Cidofovir	HSV-1
PMID: 20054446	Preclinical	Mice	2-Phenylamino-6-oxo-9-(4-hydroxybutyl) purine (HBPG)	Cidofovir	HSV-2
PMID: 20054446	Preclinical	Mice	2-Phenylamino-6-oxo-9-(4-hydroxybutyl) purine (HBPG)	Acyclovir	HSV-1
PMID: 20054446	Preclinical	Mice	2-Phenylamino-6-oxo-9-(4-hydroxybutyl) purine (HBPG)	Foscarnet	HSV-2
PMID: 2163462	Preclinical	Vero	2-Phenylamino-6-oxo-9-(4-hydroxybutyl) purine (HBPG)	Interferon beta	HSV-1
PMID: 2984988	Preclinical	RK-13	5-methoxymethyl-2'-deoxyuridine (MMUdR)	Foscarnet	HSV-1
PMID: 2984988	Precli	RK-13	5-	Foscarnet	HS

	nical		methoxymethyl-2'-deoxyuridine (MMUdR)		V-2
PMID: 2984988	Preclinical	RK-13	5-methoxymethyl-2'-deoxyuridine (MMUdR)	Trifluridine	HSV-1
PMID: 2984988	Preclinical	RK-13	5-methoxymethyl-2'-deoxyuridine (MMUdR)	Trifluridine	HSV-2
PMID: 6249191	Preclinical	RK-13; Vero	5-methoxymethyl-2'-deoxyuridine (MMUdR)	Vidarabine	HSV-1
PMID: 14231461	Preclinical	Unknown	5-methyltryptophan	Broxuridine	VACV
PMID: 6285733	Preclinical	MRC-5	5-trifluorothymidine (TFT)	Acyclovir	VZV
PMID: 6285731	Preclinical	Vero	5-trifluorothymidine (TFT)	Acyclovir	HSV-1
PMID: 6285731	Preclinical	Vero	5-trifluorothymidine (TFT)	Acyclovir	HSV-2
PMID: 6285731	Preclinical	Vero	5-trifluorothymidine (TFT)	Brivudine	HSV-1
PMID: 6285731	Preclinical	Vero	5-trifluorothymi	Brivudine	HSV-2

			dine (TFT)		
PMID: 6285731	Preclinical	Vero	5-trifluorothymidine (TFT)	Foscarnet	HSV-1
PMID: 6285731	Preclinical	Vero	5-trifluorothymidine (TFT)	Foscarnet	HSV-2
PMID: 6285731	Preclinical	Vero	5-trifluorothymidine (TFT)	Vidarabine	HSV-1
PMID: 6285731	Preclinical	Vero	5-trifluorothymidine (TFT)	Vidarabine	HSV-2
PMID: 6610387	Preclinical	Mice	9-(1,3-dihydroxy-2-propoxymethyl)guanine (DHPG)	Interferon beta	HSV-2
PMID: 23905913	0/1	Human	9-(N-methyl-L-isoleucine)-cyclosporin A (NIM811)	Ribavirin	SARS-CoV
NCT00002440	2	Human	Abacavir	Amprenavir	HIV-1
PMID: 10671335	0/1	Human	Abacavir	Amprenavir	HIV-1
NCT00002440	2	Human	Abacavir	Indinavir	HIV-1
NCT00002440	2	Human	Abacavir	Nelfinavir	HIV-1
NCT00002440	2	Human	Abacavir	Ritonavir	HIV-1
NCT00002440	2	Human	Abacavir	Saquinavir	HIV-1
NCT03576066	2	Human	ABI-H0731	Entecavir	HBV

NCT03576066	2	Human	ABI-H0731	Tenofovir	HBV
PMID: 1662957	Preclinical	Unknown	Acemannan	Acyclovir	HIV-1
PMID: 1662957	Preclinical	Unknown	Acemannan	Acyclovir	HSV-1
PMID: 1662957	Preclinical	Unknown	Acemannan	Zidovudine	HIV-1
PMID: 1662957	Preclinical	Unknown	Acemannan	Zidovudine	HSV-1
PMID: 1339152	Preclinical	CEF	Acyclovir	Quercetin	HSV-1
PMID: 1339152	Preclinical	CEF	Acyclovir	Quercetin	HSV-2
PMID: 12742576	Preclinical	FLF	Acyclovir	Lactoferrin	CMV
PMID: 31849920	Preclinical	HaCat	acyclovir	Omeprazole	HSV-1
PMID: 31849920	Preclinical	HaCat	acyclovir	Omeprazole	HSV-2
PMID: 23261844	Preclinical	HEF	Acyclovir	Amenamevir	HSV-1
PMID: 23261844	Preclinical	HEF	Acyclovir	Amenamevir	HSV-2
PMID: 23261844	Preclinical	HEF	Acyclovir	Amenamevir	VZV
PMID: 6179416	Preclinical	HEL	Acyclovir	Foscarnet	CMV
PMID: 1337893	Preclinical	HEL	Acyclovir	Cidofovir	CMV
PMID: 6179416	Preclinical	HEL	Acyclovir	Trifluridine	CMV
PMID: 1337893	Preclinical	HEL	Acyclovir	Zidovudine	CMV
PMID: 30652455	0/1	Human	Acyclovir	Foscarnet	HSV-1

PMID: 2455473	Preclinical	Mice	Acyclovir	Vidarabine	HSV-2
PMID: 21788472	Preclinical	Mice	Acyclovir	Brincidofovir	HSV-1
PMID: 21788472	Preclinical	Mice	Acyclovir	Brincidofovir	HSV-2
PMID: 12367721	Preclinical	MRC-5	Acyclovir	Docosanol	CMV
PMID: 12367721	Preclinical	MRC-5	Acyclovir	Docosanol	VZV
PMID: 6285733	Preclinical	MRC-5	Acyclovir	Foscarnet	VZV
PMID: 23261844	Preclinical	MRC-5	Acyclovir	Amenamevir	VZV
PMID: 6285733	Preclinical	MRC-5	Acyclovir	Brivudine	VZV
PMID: 6285733	Preclinical	MRC-5	Acyclovir	Vidarabine	VZV
PMID: 6285733	Preclinical	MRC-5	Acyclovir	Idoxuridine	VZV
PMID: 25779572	Preclinical	NHDF	Acyclovir	Letermovir	CMV
PMID: 2987369	Preclinical	Unknown	Acyclovir	Interferon alpha	HSV-1
PMID: 2987369	Preclinical	Unknown	Acyclovir	Interferon alpha	HSV-2
PMID: 2166426	Preclinical	Unknown	Acyclovir	Ribavirin	HSV-1
PMID: 12367721	Preclinical	Vero	Acyclovir	Docosanol	HSV-1
PMID: 12367721	Preclinical	Vero	Acyclovir	Docosanol	HSV-2
PMID: 6285731	Preclinical	Vero	Acyclovir	Foscarnet	HSV-1
PMID: 6285731	Preclinical	Vero	Acyclovir	Foscarnet	HSV-2

PMID: 23261844	Preclinical	Vero	Acyclovir	Amenamevir	HSV-2
PMID: 6285731	Preclinical	Vero	Acyclovir	Brivudine	HSV-1
PMID: 6285731	Preclinical	Vero	Acyclovir	Brivudine	HSV-2
PMID: 6285731	Preclinical	Vero	Acyclovir	Vidarabine	HSV-1
PMID: 6285731	Preclinical	Vero	Acyclovir	Vidarabine	HSV-2
PMID: 29357297	Preclinical	Vero	Acyclovir	Antibodies	HSV-1
PMID: 29357297	Preclinical	Vero	Acyclovir	Antibodies	HSV-2
PMID: 2163462	Preclinical	Vero	Acyclovir	Interferon beta	HSV-1
PMID: 19374144	Preclinical	AD38	Adefovir	Tenofovir	HBV
PMID: 15388423	Preclinical	HepG2	Adefovir	Entecavir	HBV
PMID: 15388423	Preclinical	HepG2	Adefovir	Tenofovir	HBV
PMID: 10681317	Preclinical	Huh7	Adefovir	lamivudine	HBV
PMID: 10681317	Preclinical	Huh7	Adefovir	Penciclovir	HBV
NCT01263002	4	Human	Adefovir	Clevudine	HBV
PMID: 23650173;NCT01023217	4	Human	Adefovir	Entecavir	HBV
NCT02366208	2	Human	Adefovir	Interferon alpha	HBV
NCT00922207	4	Human	Adefovir	Interferon alpha	HBV
PMID: 23650172;NCT01023217	4	Human	Adefovir	Lamivudine	HBV

NCT00002326	1	Human	Adefovir	Zidovudine	HIV
PMID: 29652799	Preclinical	H2.36	Adezmapimod	rapamycin	RVFV
PMID: 28063993	Preclinical	RD; Vero; HEK-293T	ALD	NK-1.9k	EV-A71
NCT00001005	1	Human	Aldesleukin	Zidovudine	HIV
PMID: 25305505	Preclinical	HepG2215	Alisporivir	Telbivudine	HBV
PMID: 24687498	Preclinical	Huh7	Alisporivir	Boceprevir	HCV
PMID: 24687498	Preclinical	Huh7	Alisporivir	Daclatasvir	HCV
PMID: 24687498	Preclinical	Huh7	Alisporivir	Mericitabine	HCV
PMID: 24687498	Preclinical	Huh7	Alisporivir	Sofosbuvir	HCV
PMID: 24687498	Preclinical	Huh7	Alisporivir	Telaprevir	HCV
NCT02094443	2	Human	Alisporivir	Ribavirin	HCV
PMID: 26118427	2	Human	Alisporivir	ribavirin	HCV
PMID: 23905913	0/1	Human	Alisporivir	Ribavirin	SARS-CoV
PMID: 20112171	2	Human	Alisporivir	Interferon alpha	HCV
PMID: 27840112	Preclinical	Mice	Alisporivir	ribavirin	MERS-CoV
PMID: 27840112	Preclinical	Mice	Alisporivir	ribavirin	SARS-CoV
PMID: 18043443	0/1	Human	Alivizumab	Ribavirin	RSV

PMID: 27341844	Preclinical	Mice	Alpha-tocopherol	Oseltamivir	FLUAV
NCT00000743	1	Human	Alvircept sudotox	Zidovudine	HIV
PMID: 19273672	Preclinical	MDCK	Amantadine	Ribavirin	FLUAV
PMID: 23820269	Preclinical	MDCK	Amantadine	Diphyllin	FLUAV
PMID: 19273672	Preclinical	MDCK	Amantadine	Oseltamivir	FLUAV
PMID: 7396454	Preclinical	Mice	Amantadine	Ribavirin	FLUAV
PMID: 7396454	Preclinical	Mice	Amantadine	Ribavirin	FLUBV
PMID: 17591026	Preclinical	Mice	Amantadine	Oseltamivir	FLUAV
PMID: 16206613	Preclinical	Unknown	Amantadine	Arbidol	FLUAV
PMID: 20386073;NCT00432016	2	Human	Amdoxovir	Zidovudine	HIV
PMID: 23261844	Preclinical	MRC-5	Amenamevir	Penciclovir	VZV
PMID: 23261844	Preclinical	MRC-5	Amenamevir	Vidarabine	VZV
PMID: 23261844	Preclinical	Vero	Amenamevir	Penciclovir	HSV-2
PMID: 23261844	Preclinical	Vero	Amenamevir	Vidarabine	HSV-2
PMID: 23127366	Preclinical	A549	amiRNA	Cidofovir	HAdV
PMID: 27565991	Preclinical	Vero	amiRNA	Chloroquine	CHIKV
PMID: 27565991	Preclinical	Vero	amiRNA	Mycophenolic acid	CHIKV
PMID: 27565991	Preclinical	Vero	amiRNA	Ribavirin	CHIKV
PMID: 22445690	Precli	Mice	ammonium	Antibodies	WN

	nical		trichloro(dioxyethylene-0-0')tellurate (AS101)		V
PMID: 26735991	0/1	Human	Amodiaquine	Artesunate	EBOV
PMID: 32805422	Preclinical	Vero	Amodiaquine	Artesunate	SARS-CoV-2
PMID: 33333292	Preclinical	Vero	Amodiaquine	Lopinavir	SARS-CoV-2
PMID: 33333292	Preclinical	Vero	Amodiaquine	Nitazoxanide	SARS-CoV-2
PMID: 33333292	Preclinical	Vero	Amodiaquine	Remdesivir	SARS-CoV-2
PMID: 33333292	Preclinical	Vero	Amodiaquine	Umifenovir	SARS-CoV-2
PMID: 10671334	0/1	Human	Amprenavir	Efavirenz	HIV-1
PMID: 15728914	0/1	Human	Amprenavir	Fosamprenavir	HIV-1
PMID: 15728914	0/1	Human	Amprenavir	Ritonavir	HIV-1
PMID: 15889535	Preclinical	Unknown	Amylmetacresol	Dichlorobenzyl alcohol	FLUAV
PMID: 15889535	Preclinical	Unknown	Amylmetacresol	Dichlorobenzyl alcohol	RSV

PMID: 15889535	Preclinical	Unknown	Amylmetacresol	Dichlorobenzyl alcohol	SARS-CoV
PMID: 30621343	Preclinical	293T; Huh-7	Antibodies	HR2P-M2	MERS-CoV
PMID: 7474167	Preclinical	AT3	Antibodies	Interferon alpha	SINV
PMID: 3550674	Preclinical	Cotton rat	Antibodies	Ribavirin	RSV
PMID: 6715898	Preclinical	cynomolgus monkeys	Antibodies	Ribavirin	LASV
PMID: 28633457	Preclinical	Ferrets	Antibodies	Oseltamivir	FLUAV
PMID: 16796401	Preclinical	FRhK-4	Antibodies	Antibodies	SARS-CoV
PMID: 23616649	Preclinical	Guinea pigs	Antibodies	Antibodies	EBOV
PMID: 19591879	Preclinical	HMF; Hela Cells	Antibodies	siRNA	HEV-B
ChiCTR2000030580	0/1	Human	Antibodies	Antibodies	SARS-CoV-2
NCT00001999	0/1	Human	Antibodies	Ganciclovir	CMV
PMID: 19344395	0/1	Human	Antibodies	Ribavirin	HMPV
PMID: 21826009;NCT00639938	3	Human	Antibodies	Nevirapine	HIV
PMID: 12692287	0/1	Human	Antibodies	Pleconaril	PV
PMID: 30071205	Preclinical	Mice	Antibodies	Sunitinib	DENV

PMID: 23125446	Preclinical	Mice	Antibodies	Antibodies	CHIKV
PMID: 28148840	Preclinical	Mice	Antibodies	Antibodies	CHIKV
PMID: 16227266	Preclinical	Mice	Antibodies	Antibodies	VACV
PMID: 20587859	Preclinical	Mice	Antibodies	Antibodies	VACV
PMID: 17376910	Preclinical	Mice	Antibodies	Interferon gamma	SINV
PMID: 25193982	Preclinical	Mice	Antibodies	siRNA	HEV-B
PMID: 24824031	Preclinical	Unknown	Antibodies	Antibodies	PV
PMID: 11517408	Preclinical	SVG-A	Antibodies	Chlorpromazine	JCV
PMID: 25451066	Preclinical	Unknown	Antibodies	Antibodies	MERS-CoV
PMID: 1665535	Preclinical	Unknown	Antibodies	Interferon alpha	PV
PMID: 30518644	Preclinical	Unknown	Antibodies	Fostemsavir	HIV-1
PMID: 26354735	Preclinical	Unknown	Antibodies	Maraviroc	HIV-1
PMID: 29357297	Preclinical	Vero	Antibodies	Ganciclovir	HSV-1
PMID: 29357297	Preclinical	Vero	Antibodies	Ganciclovir	HSV-2
PMID: 29357297	Preclinical	Vero	Antibodies	Foscarnet	HSV-1
PMID: 29357297	Preclinical	Vero	Antibodies	Foscarnet	HSV-2
PMID: 29357297	Preclinical	Vero	Antibodies	Penciclovir	HSV-1
PMID: 29357297	Precli	Vero	Antibodies	Penciclovir	HS

	nical				V-2
PMID: 6190753	Preclinical	WISH cells; RK-13	Antibodies	Interferon gamma	HAdV
PMID: 6190753	Preclinical	WISH cells; RK-13	Antibodies	Interferon gamma	HDV
PMID: 6190753	Preclinical	WISH cells; RK-13	Antibodies	Interferon gamma	HSV-1
PMID: 6190753	Preclinical	WISH cells; RK-13	Antibodies	Interferon beta	HAdV
PMID: 6190753	Preclinical	WISH cells; RK-13	Antibodies	Interferon beta	HDV
PMID: 6190753	Preclinical	WISH cells; RK-13	Antibodies	Interferon beta	HSV-1
NCT02452528	2	Human	Antigen	Entecavir	HBV
NCT02431312	1	Human	Antigen	Interleukin 12	HBV
PMID: 12087926	Preclinical	Vero	Aphidicolin	Cidofovir	HSV-1
PMID: 33801811	Preclinical	Huh7	Apilimod	Azithromycin	EBOV
PMID: 33801811	Preclinical	Huh7	Apilimod	Clomiphene	EBOV
PMID: 33801811	Preclinical	Huh7	Apilimod	Toremifene	EBOV
PMID: 2434613	Preclinical	Mice	Aprotinin	Rimantadine	FLUAV
NCT04273763	0/1	Human	Arbidol	Interferon alpha	SARS-CoV

					-2
ChiCTR2000029573	0/1	Human	Arbidol	Novaferon	SARS-CoV-2
PMID: 16206613	Preclinical	Unknown	Arbidol	Ribamidil	FLUAV
PMID: 16206613	Preclinical	Unknown	Arbidol	Ribavirin	FLUAV
PMID: 16206613	Preclinical	Unknown	Arbidol	Rimantadine	FLUAV
PMID: 32637956;https://doi.org/10.1101/2020.06.29.178889	Preclinical	Vero-E6 cells	Arbidol	Nitazoxanide	SARS-CoV-2
NCT02452528	2	Human	ARC-520	Tenofovir	HBV
NCT02577029	2	Human	ARC-520	Tenofovir	HBV
PMID: 15026197	Preclinical	Cell cultures	Arildone	N-phenyl-N′-3-hydroxyphenylthiourea (PTU-23)	CVB-1
PMID: 10757231	Preclinical	FL cells	Arildone	N-phenyl-N′-3-hydroxyphenylthiourea (PTU-23)	PV
PMID: 10757231	Preclinical	FL cells	Arildone	Enviroxime	PV
PMID: 33801811	Preclinical	Huh7	Aripiprazole	Piperacetazine	EBOV
PMID: 33801811;PMID: 29939303	Preclinical	Vero-E6; Huh-7;	Aripiprazole	Piperacetazine	EBOV

		HEK293T/19			
PMID: 32805422	Preclinical	Vero	Artemether	Lumefantrine	SARS-CoV-2
PMID: 32805422	Preclinical	Vero	Artemether	pyronaridine	SARS-CoV-2
PMID: 32805422	Preclinical	Vero E6 cells	artemether	lumefantrine	SARS-CoV-2
PMID: 32805422	Preclinical	Vero	Artenimol	piperaquine	SARS-CoV-2
PMID: 32805422	Preclinical	Vero E6 cells	Artenimol	piperaquine	SARS-CoV-2
PMID: 24277030	Preclinical	HFF	Artesunate	Sunitinib	CMV
PMID: 26374952	Preclinical	Mice	Artesunate	Rapamycin	HIV-1
PMID: 26374952	Preclinical	Mice	Artesunate	Valacyclovir	HIV-1
PMID: 26844400	Preclinical	MRC-5	Artesunate	Cidofovir	CMV
PMID: 26844400	Preclinical	MRC-5	Artesunate	Foscarnet	CMV
PMID: 26844400	Preclinical	MRC-5	Artesunate	ganciclovir	CMV
PMID: 26844400	Preclinical	MRC-5	Artesunate	Letermovir	CMV

PMID: 26844400	Preclinical	MRC-5	Artesunate	Maribavir	CMV
PMID: 32805422	Preclinical	Vero	Artesunate	Mefloquine	SARS-CoV-2
PMID: 32805422	Preclinical	Vero	Artesunate	pyronaridine	SARS-CoV-2
NCT04261907	0/1	Human	ASC09	Ritonavir	SARS-CoV-2
PMID: 26683763;NCT01012895	2	Human	Asunaprevir	Daclatasvir	HCV
PMID: 23274666	Preclinical	Unknown	Asunaprevir	Interferon lambda	HCV
NCT00272779	3	Human	Atazanavir	Ritonavir	HIV
NCT00384904	4	Human	Atazanavir	Ritonavir	HIV
NCT00874523	3	Human	Atazanavir	Raltegravir	HIV
PMID: 32759267	Preclinical	Vero	Atazanavir	Ritonavir	SARS-CoV-2
NCT00002322	2	Human	Atevirdine	Zidovudine	HIV
PMID: 27117260	Preclinical	U373-MAGI	Azacitidine	Clofarabine	HIV-1
PMID: 27117260	Preclinical	U373-MAGI	Azacitidine	Gemcitabine	HIV-1
PMID: 27117260	Preclinical	U373-MAGI	Azacitidine	Hydroxyurea	HIV-1
PMID: 27117260	Preclinical	U373-MAGI	Azacitidine	Resveratrol	HIV-1
PMID: 23523553	Preclinical	A549	AZD-8330	Oseltamivir	FLUAV

PMID: 31806372	Preclinical	HEK293T	Azithromycin	Digitoxin	EBOV
PMID: 31806372	Preclinical	HEK293T	Azithromycin	Fluvastatin	EBOV
PMID: 32205204;DOI : 10.1016/j.ijantimicag.2020.105949	3	Human	Azithromycin	Hydroxychloroquine	SARS-CoV-2
PMID: 24632748;UMIN000005371	2	Human	Azithromycin	Oseltamivir	FLUAV
PMID: 33049959	Preclinical	MDCK	Baloxavir marboxil	favipiravir	FLUAV
PMID: 33049959	Preclinical	MDCK	Baloxavir marboxil	oseltamivir	FLUAV
PMID: 33049959	Preclinical	MDCK	Baloxavir marboxil	Peramivir	FLUAV
PMID: 33049959	Preclinical	MDCK	Baloxavir marboxil	ribavirin	FLUAV
PMID: 33049959	Preclinical	MDCK	Baloxavir marboxil	zanamivir	FLUAV
PMID: 33049959	Preclinical	ST6-GalI-MDCK cells	Baloxavir marboxil	peramivir	FLUAV
PMID: 30476172	Preclinical	Mice	Baloxavir marboxil	Oseltamivir	FLUAV
NCT01273948	2	Human	Bavituximab	Ribavirin	HCV
PMID: 33801811	Preclinical	Huh7	Bepridil	Sertraline	EBOV
PMID: 29652799	Preclinical	H2.35	BI-D1870	PF-4708671	RVFV
PMID: 26902761;NCT01009814	2	Human	BMS-663068	Ritonavir	HIV-1
PMID: 27035622	Preclinical	Huh7	Boceprevir	Daclatasvir	HCV

PMID: 27035622	Preclinical	Huh7	Boceprevir	Sofosbuvir	HCV
PMID: 27035622	Preclinical	Huh7	Boceprevir	Telaprevir	HCV
PMID: 30153445	Preclinical	HFF	Brincidofovir	Letermovir	CMV
PMID: 17724153	Preclinical	Mice	Brincidofovir	Tecovirimat	VACV
PMID: 28827083	Preclinical	Syrian hamsters	Brincidofovir	Valganciclovir	HAdV
PMID: 26036224	Preclinical	Huh 9-13; HuH6; Huh 5-2 cells	Brivudine	Tegobuvir	HCV
PMID: 6329083	Preclinical	Human embryonic fibroblasts	Brivudine	Interferon alpha	VZV
PMID: 6285731	Preclinical	Vero	Brivudine	Foscarnet	HSV-1
PMID: 6285731	Preclinical	Vero	Brivudine	Foscarnet	HSV-2
PMID: 6285731	Preclinical	Vero	Brivudine	Vidarabine	HSV-1
PMID: 6285731	Preclinical	Vero	Brivudine	Vidarabine	HSV-2
PMID: 14231461	Preclinical	Unknown	Broxuridine	Noformicin	VACV
PMID: 21466823	Preclinical	Unknown	BTA798	Rupintrivir	EV-A71
PMID: 21466823	Preclinical	Unknown	BTA798	Rupintrivir	HRV-B14

PMID: 21466823	Preclinical	Unknown	BTA798	Rupintrivir	PV
PMID: 7905523;NCT00001993	2	Human	Butyldeoxynojirimycin	Zidovudine	HIV
PMID: 19616097	Preclinical	Mice	Caffeine	Lovastatin	FLUAV
PMID: 15068455	0/1	Human	Cantharidin	Imiquimod	MCV
PMID: 9477119	Preclinical	L929 cells	Carbenoxolone	Prostaglandin A1	VACV
PMID: 1333651	Preclinical	Vero cells	Carbocyclic oxetanocin G	Oxetanocin G	HSV-1
PMID: 1333651	Preclinical	Vero cells	Carbocyclic oxetanocin G	Oxetanocin G	HSV-2
PMID: 26053018	Preclinical	MDCK	Carrageenan	Zanamivir	FLUAV
PMID: 26636929	2	Human	Cenicriviroc	efavirenz	HIV-1
PMID: 24040429	Preclinical	Mice	Chik-5 siRNA	siRNA	CHIKV
PMID: 24040429	Preclinical	Vero cells	Chik-5 siRNA	siRNA	CHIKV
PMID: 27035622	Preclinical	Huh7.5.1; Con1b cells	Chlorcyclizine	Telaprevir	HCV
PMID: 30711416;NCT02118012	1	Human	Chlorcyclizine	Ribavirin	HCV
PMID: 31806372	Preclinical	HEK293T	Chloroquine	Fluvastatin	EBOV
PMID: 31806372	Preclinical	HEK293T	Chloroquine	Tetradrine	EBOV
NCT04303299	3	Human	Chloroquine	Oseltamivir	SARS-CoV-2

PMID: 25796972	Preclinical	Vero	Chloroquine	Ribavirin	CCHFV
PMID: 25796972	Preclinical	Vero	Chlorpromazine	Ribavirin	CCHFV
PMID: 26752302	Preclinical	293 T cells	Cidofovir	Zidovudine	EBOV
PMID: 26752302	Preclinical	293 T cells	Cidofovir	Favipiravir	EBOV
PMID: 26752302	Preclinical	293 T cells	Cidofovir	Interferon alpha	EBOV
PMID: 26752302	Preclinical	293 T cells	Cidofovir	Interferon beta	EBOV
PMID: 26752302	Preclinical	293 T cells	Cidofovir	Lamivudine	EBOV
PMID: 26752302	Preclinical	293 T cells	Cidofovir	Tenofovir	EBOV
PMID: 26752302	Preclinical	293 T cells	Cidofovir	Toremifene	EBOV
PMID: 30040968	Preclinical	ARPEp	Cidofovir	Maribavir	CMV
PMID: 17042327	Preclinical	CEF	Cidofovir	Idoxuridine	VACV
PMID: 12742576	Preclinical	FLF	Cidofovir	Lactoferrin	CMV
PMID: 1337893	Preclinical	HEL	Cidofovir	Foscarnet	CMV
PMID: 1337893	Preclinical	HEL	Cidofovir	Zidovudine	CMV
PMID: 1337893	Preclinical	HEL	Cidofovir	Ganciclovir	CMV
PMID: 19307376	Preclinical	HEL	Cidofovir	siRNA	VACV
PMID: 17516391	0/1	Human	Cidofovir	Foscarnet	HHV-6

PMID: 25385098	Preclinical	Mice	Cidofovir	VIG	VACV
PMID: 25779572	Preclinical	NHDF	Cidofovir	Letermovir	CMV
NCT01264367	4	Human	Clevudine	Interferon alpha	HBV
NCT00798460	4	Human	Clevudine	Lamivudine	HBV
NCT00823342	3	Human	Clevudine	Tenofovir	HBV
PMID: 33801811	Preclinical	Huh7	Clomiphene	Sertraline	EBOV
PMID: 32671131;NCT04252274	3	Human	Cobicistat	Darunavir	SARS-CoV-2
PMID: 31769793;NCT03045861	2	Human	Cobicistat	GSK2838232	HIV-1
PMID: 6636703	Preclinical	Pig embryo kidney cells	Cycloheximide	Dactinomycin	TBEV
PMID: 28807916	Preclinical	HG23	Cyclosporine	Mycophenolic acid	NoV
PMID: 28807916	Preclinical	HG23	Cyclosporine	Ribavirin	NoV
PMID: 28807916	Preclinical	HG23	Cyclosporine	Tacrolimus	NoV
NCT02328963	4	Human	Cyclosporine	Mycophenolic acid	CMV
PMID: 15540900	0/1	Human	Cyclosporine	HDIG	B19V
PMID: 29772254	Preclinical	Human lung microvascular	Cyclosporine	Interferon alpha	MERS-CoV

		endothelial cells			
PMID: 17101321	Preclinical	Vero	Cyclosporine	Mycophenolic acid	HCV
NCT00002110	2	Human	Cysteamine	Zidovudine	HIV
PMID: 27035622	Preclinical	Huh7	Daclatasvir	Sofosbuvir	HCV
PMID: 31594756	Preclinical	Huh7	Daclatasvir	Sofosbuvir	YFV
PMID: 23274666	Preclinical	Huh7	Daclatasvir	Interferon lambda	HCV
PMID: 24687498	Preclinical	Huh7	Daclatasvir	Sanglifehrin B	HCV
PMID: 27035622	Preclinical	Huh7	Daclatasvir	Telaprevir	HCV
PMID: 25614962;NCT02032901	3	Human	Daclatasvir	Sofosbuvir	HCV
PMID: 31504303;NCT03200184	4	Human	Daclatasvir	Sofosbuvir	HCV
NCT01425970	2	Human	Daclatasvir	INX-08189	HCV
PMID: 26453967;NCT01628692	2	Human	Daclatasvir	Simeprevir	HCV
PMID: 31024969;NCT02469298	2	Human	Danirixin	Oseltamivir	FLUAV
PMID: 20951424;NCT00801255	1	Human	Danoprevir	Mericitabine	HCV
NCT04291729	4	Human	Danoprevir	Ritonavir	SARS-CoV-2
ChiCTR2000030259	0/1	Human	Danorevir	ritonavir	SARS-CoV-2
PMID: 21633286	Precli	TZM-bl	Dapivirine	Tenofovir	HIV

	nical				-1
NCT00355524	2	Human	Darunavir	Ritonavir	HIV -1
PMID: 23088336;NCT00258557	3	Human	Darunavir	Ritonavir	HIV -1
PMID: 27117260	Preclinical	HEK-293T	Decitabine	Resveratrol	HIV -1
PMID: 27117260	Preclinical	U373-MAGI	Decitabine	Resveratrol	HIV -1
NCT01859962	2	Human	Deleobuvir	Ravidasvir	HCV
NCT00001022	3	Human	Didanosine	Zidovudine	HIV
PMID: 7727768	2	Human	Didanosine	Zidovudine	HIV -1
PMID: 15597521;NCT00001074	1	Human	Didanosine	Hydroxyurea	HIV
PMID: 8721897;NCT00002098	1	Human	Didanosine	Lentinan	HIV
NCT00001997	0/1	Human	Didanosine	PEG IL-2	HIV
NCT00000833	1	Human	Didanosine	Ribavirin	HIV
PMID: 10449279;NCT00002207	0/1	Human	Didanosine	Stavudine	HIV
NCT00002109	3	Human	Didanosine	Timunox	HIV
PMID: 23933116	Preclinical	MRC-5	Didox	Ganciclovir	CMV
PMID: 31806372	Preclinical	HEK293T	Digitoxin	Fluvastatin	EBOV
PMID: 31806372	Preclinical	HEK293T	Digitoxin	Tamoxifen	EBOV
PMID: 31806372	Preclinical	HEK293T	Digitoxin	Tetradrine	EBOV
PMID: 31806372	Preclinical	HEK293T; HeLa; THP-4	Digitoxin	tetrandrine	EBOV
PMID: 24277030	Preclinical	HFF	Digitoxin	Ganciclovir	CMV
PMID: 24277030	Preclinical	HFF	Digoxin	Ganciclovir	CMV

PMID: 1964373	Preclinical	Raji; Raji-HSV	Dinoprostone	Interferon alpha	HSV-1
PMID: 1964373	Preclinical	Vero	Dinoprostone	Indomethacin	HSV-1
PMID: 23820269	Preclinical	MDCK	Diphyllin	Oseltamivir	FLUAV
PMID: 32711800	3	Human	disoproxil fumarate	Emtricitabine	HIV-1
PMID: 15026197	Preclinical	Cell cultures	Disoxaril	N-Phenyl-N'-3-hydroxyphenylthiourea (PTU-23)	CVB-1
PMID: 10757231	Preclinical	FL cells	Disoxaril	N-Phenyl-N'-3-hydroxyphenylthiourea (PTU-23)	PV
PMID: 10757231	Preclinical	FL cells	Disoxaril	Enviroxime	PV
PMID: 12367721	Preclinical	Vero	Docosanol	Foscarnet	HSV-1
PMID: 12367721	Preclinical	Vero	Docosanol	ribavirin	HSV-1
PMID: 12367721	Preclinical	Vero	Docosanol	Trifluridine	HSV-1
PMID: 12367721	Preclinical	Vero	Docosanol	Vidarabine	HSV-1
PMID: 30668695;NCT02582684	2	Human	Dolutegravir	Lamivudine	HIV-1
NCT01910402	3	Human	Dolutegravir	Lamivudine	HIV-1
PMID: 30420123	3	Human	Dolutegravir	Lamivudine	HIV-1
NCT02211482	4	Human	Dolutegravir	Lamivudine	HIV

					-1
PMID: 31307948;NCT02422797	3	Human	Dolutegravir	Rilpivirine	HIV-1
PMID: 31121013;NCT01632345	2	Human	Doravirine	Emtricitabine	HIV
PMID: 25331113	2	Human	Doxorubicin	Rituximab	KSHV
PMID: 25970853	Preclinical	Vero	Doxycycline	Ribavirin	CHIKV
PMID: 6151353	Preclinical	Unknown	Edoxudine	Quercetin	HSV-1
NCT00002387	0/1	Human	Efavirenz	Indinavir	HIV-1
PMID: 28760340	Preclinical	U2OS	EGCG	Suramin	CHIKV
PMID: 27542322	3	Human	Elbasvir	Grazoprevir	HCV
PMID: 32383275	3	Human	elbasvir	grazoprevir	HCV
PMID: 31765046;NCT03111108	4	Human	Elbasvir	Grazoprevir	HCV
PMID: 32637956;https://doi.org/10.1101/2020.06.29.178889	Preclinical	Vero-E6 cells	Ementine	Nitazoxanide	SARS-CoV-2
PMID: 31635418	Preclinical	RPE	Emetine	Obatoclax	FLUAV
PMID: 33333292	Preclinical	Vero	Emetine	Nitazoxanide	SARS-CoV-2
PMID: 27571349	Preclinical	human astrocytes	Emricasan	Niclosamide	ZIKV
PMID: 27571349	Preclinical	Unknown	Emricasan	PHA-690509	ZIKV
PMID: 19374144	Precli	AD38	Emtricitabine	Tenofovir	HB

	nical				V
PMID: 21254162;NCT00298363	2	Human	Emtricitabine	Tenofovir	HBV
PMID: 32711800	3	Human	Emtricitabine	tenofovir	HIV-1
NCT00362687	4	Human	Emtricitabine	Tenofovir	HIV-1
NCT00312546	1	Human	Enfuvirtide	Valproic acid	HIV-1
PMID: 19374144	Preclinical	AD38	Entecavir	Tenofovir	HBV
NCT02360592	4	Human	Entecavir	Interferon alpha	HBV
NCT03509688	2	Human	Entecavir	Resveratrol	HBV
NCT00994773	1	Human	Entecavir	Simvastatin	HBV
NCT00605384	3	Human	Entecavir	Tenofovir	HBV
NCT01639066	4	Human	Entecavir	Tenofovir	HBV
PMID: 25800784	4	Human	entecavir	tenofovir	HBV
NCT01938820	4	Human	Entecavir	Thymosin a1	HBV
PMID: 15026197	Preclinical	Cell cultures	Enviroxime	Ethyl 4-methyl-2-(methylthio)pyrimidine-5-carboxylate	CVB-1
PMID: 15026197	Preclinical	Cell cultures	Enviroxime	N-Phenyl-N'-3-hydroxyphenylthiourea (PTU-23)	CVB-1
PMID: 10757231	Precli	FL cells	Enviroxime	Ethyl 4-	PV

	nical			methyl-2-(methylthio)pyrimidine-5-carboxylate	
PMID: 10757231	Preclinical	FL cells	enviroxime	Guanidine	PV
PMID: 21466823	Preclinical	Unknown	Enviroxime	Ribavirin	EV-A71
PMID: 21466823	Preclinical	Unknown	Enviroxime	Ribavirin	HRV-B14
PMID: 21466823	Preclinical	Unknown	Enviroxime	Ribavirin	PV
PMID: 3017203	Preclinical	WISH cells	Enviroxime	Interferon gamma	HRV-A2
PMID: 24416771	Preclinical	Mice	Etanercept	Valacyclovir	HSV-1
PMID: 27966790	Preclinical	Mice	Eucalyptol	Oseltamivir	FLUAV
PMID: 28247521	0/1	Human	Everolimus	Leflunomide	BKV
NCT02716428	2	Human	Faldaprevir	TD-6450	HCV
PMID: 12195876;PMID: 10915748	2	Human	famciclovir	lamivudine	HBV
PMID: 26752302	Preclinical	293 T cells	Favipiravir	Interferon alpha	EBOV
PMID: 26752302	Preclinical	293 T cells	Favipiravir	Interferon beta	EBOV
PMID: 26752302	Preclinical	293 T cells	Favipiravir	Lamivudine	EBOV
PMID: 26752302	Preclinical	293 T cells	Favipiravir	Tenofovir	EBOV
PMID: 26752302	Preclinical	293 T cells	Favipiravir	Toremifene	EBOV

PMID: 26752302	Preclinical	293 T cells	Favipiravir	Zidovudine	EBOV
PMID: 32135218	Preclinical	cynomolgus macaques	Favipiravir	Ribavirin	EBOV
PMID: 26711718	Preclinical	Guinea pigs	Favipiravir	Ribavirin	JUNV
PMID: 24486952	Preclinical	Hamsters	Favipiravir	Ribavirin	RVFV
PMID: 24890597	Preclinical	HG23	Favipiravir	Rupintrivir	NoV
PMID: 34040117;ChiCTR2000029600	0/1	Human	Favipiravir	Interferon alpha	SARS-CoV-2
NCT03394209	2	Human	Favipiravir	Oseltamivir	FLUAV
PMID: 3337898;ChiCTR2000030894	4	Human	Favipiravir	Tocilizumab	SARS-CoV-2
PMID: 24311151	Preclinical	MDCK	Favipiravir	Oseltamivir	FLUAV
PMID: 24311151	Preclinical	MDCK	Favipiravir	Peramivir	FLUAV
PMID: 25547360	Preclinical	MDCK	Favipiravir	Pimodivir	FLUAV
PMID: 24311151	Preclinical	MDCK	Favipiravir	Zanamivir	FLUAV
PMID: 24786461	Preclinical	Mice	Favipiravir	Ribavirin	CCHFV
PMID: 26531247	Preclinical	Mice	Favipiravir	Ribavirin	LASV
PMID: 24992479	Precli	Mice	Favipiravir	Peramivir	FLU

	nical				AV
PMID: 22429564	Preclinical	Mice	Favipiravir	Peramivir	FLUAV
PMID: 27353263	Preclinical	RD	Favipiravir	Rupintrivir	EV-A71
PMID: 27353263	Preclinical	RD	Favipiravir	Itraconazole	EV-A71
PMID: 27353263	Preclinical	RD	Favipiravir	Suramin	EV-A71
PMID: 33540830	Preclinical	SK-N-MC	favipiravir	Interferon alpha	CHIKV
PMID: 29109164	Preclinical	Vero	Favipiravir	Ribavirin	ZIKV
PMID: 29109164	Preclinical	Vero	Favipiravir	Interferon alpha	ZIKV
PMID: 29126899	Preclinical	Vero	Favipiravir	Merimepodib	EBOV
PMID: 25274854	Preclinical	Mice	Fenofibrate	Oseltamivir	FLUAV
PMID: 25274854	Preclinical	Mice	Fenofibrate	Simvastatin	FLUAV
PMID: 31806372	Preclinical	HEK293T	Fluvastatin	Tamoxifen	EBOV
NCT00002156	2	Human	Fomivirsen	Ganciclovir	CMV
NCT00144833	3	Human	Fosamprenavir	Ritonavir	HIV-1
PMID: 30040968	Preclinical	ARPEp	Foscarnet	Maribavir	CMV
PMID: 12742576	Preclinical	FLF	Foscarnet	Lactoferrin	CMV
PMID: 1337893	Preclinical	HEL	Foscarnet	Zidovudine	CMV
PMID: 24277030	Preclinical	HFF	Foscarnet	Ganciclovir	CMV
NCT00000136	3	Human	Foscarnet	Ganciclovir	CM

					V
PMID: 16688677	0/1	Human	Foscarnet	Leflunomide	CMV
PMID: 2559657	Preclinical	MRC-5	Foscarnet	Ganciclovir	CMV
PMID: 25779572	Preclinical	NHDF	Foscarnet	Letermovir	CMV
PMID: 2559657	Preclinical	Vero	Foscarnet	Ganciclovir	HSV-2
PMID: 6285731	Preclinical	Vero	Foscarnet	Vidarabine	HSV-1
PMID: 6285731	Preclinical	Vero	Foscarnet	Vidarabine	HSV-2
PMID: 30040968	Preclinical	ARPEp	Ganciclovir	Maribavir	CMV
PMID: 12742576	Preclinical	FLF	Ganciclovir	Lactoferrin	CMV
PMID: 1337893	Preclinical	HEL	Ganciclovir	Zidovudine	CMV
PMID: 24277030	Preclinical	HFF	Ganciclovir	Ouabain	CMV
NCT00002156	2	Human	Ganciclovir	ISIS 2922	CMV
PMID: 23933116	Preclinical	MRC-5	Ganciclovir	Hydroxyurea	CMV
PMID: 12323400	Preclinical	MRC-5	Ganciclovir	Maribavir	CMV
PMID: 26844400	Preclinical	MRC-5	ganciclovir	maribavir	CMV
PMID: 23933116	Preclinical	MRC-5	Ganciclovir	Trimidox	CMV
PMID: 25779572	Preclinical	NHDF	Ganciclovir	Letermovir	CMV
PMID: 2987369	Preclinical	Unknown	Ganciclovir	Interferon alpha	HSV-1
PMID: 2987369	Precli	Unkno	Ganciclovir	Interferon	HS

	nical	wn		alpha	V-2
PMID: 20194528	Preclinical	Unknown	Ganciclovir	Mizoribine	CMV
PMID: 29795047	Preclinical	Huh7	Gemcitabine	Saracatinib	MERS-CoV
PMID: 27451344	Preclinical	Human primary macrophages	Gemcitabine	Pimodivir	FLUAV
PMID: 28049006	Preclinical	RPE	Gemcitabine	Obatoclax	ZIKV
PMID: 28049006	Preclinical	RPE	Gemcitabine	Saliphenylhalamide	ZIKV
PMID: 26526589	Preclinical	Vero	Gemcitabine	Ribavirin	CVB-3
PMID: 26526589	Preclinical	Vero	Gemcitabine	Ribavirin	EV-A71
PMID: 21947546	Preclinical	HEK 293	Genistein	Tyrphostin	EBOV
PMID: 21947546	Preclinical	Vero	Genistein	Tyrphostin	LASV
PMID: 27456384	2	Human	glecaprevir	pibrentasvir	HCV
PMID: 29020583;NCT02651194	3	Human	Glecaprevir	Pibrentasvir	HCV
PMID: 32445613	3	Human	glecaprevir	pibrentasvir	HCV
PMID: 33333254;https://www.preprints.org/manuscript/202002.0395/v1	0/1	Human	Glucocorticoid	Thalidomide	SARS-CoV-2
NCT00000791	2	Human	Glycovir	Zidovudine	HIV-1
PMID: 9477119	Preclinical	L929 cells	glycyrrhizic acid	Prostaglandin A1	VACV

PMID: 26668995	Preclinical	Mice	Glycyrrhizin	Ribavirin	FLUAV
PMID: 27291249;NCT01716156	2	Human	Grazoprevir	Ribavirin	HCV
NCT01072695	2	Human	GS-9256	Tegobuvir	HCV
PMID: 30040968	Preclinical	ARPEp	GW275175X	Maribavir	CMV
PMID: 27353263	Preclinical	RD	GW5074	Itraconazole	EV-A71
PMID: 9952383;NCT00002357	2	Human	HBY 097	Zidovudine	HIV
PMID: 26164863	Preclinical	Mice	HR2P-M2	Interferon beta	MERS-CoV
PMID: 33333292	Preclinical	Vero	Hydroxychloroquine	Lopinavir	SARS-CoV-2
PMID: 33333292	Preclinical	Vero	Hydroxychloroquine	Remdesivir	SARS-CoV-2
PMID: 33333292	Preclinical	Vero	Hydroxychloroquine	Umifenovir	SARS-CoV-2
PMID: 2163462	Preclinical	Vero	Idoxuridine	Interferon beta	HSV-1
NCT00002452	2	Human	Indinavir	L-756423	HIV
NCT00002375	0/1	Human	Indinavir	Nelfinavir	HIV
NCT00002361	2	Human	Indinavir	Ritonavir	HIV
PMID: 1964373	Preclinical	Vero	Indomethacin	Interferon alpha	HSV-1
PMID: 1711269	Preclinical	Mice	Inosine	Rimantadine	FLUAV
PMID: 26752302	Precli	293 T	Interferon	Lamivudine	EB

	nical	cells	alpha		OV
PMID: 26752302	Preclinical	293 T cells	Interferon alpha	Tenofovir	EBOV
PMID: 26752302	Preclinical	293 T cells	Interferon alpha	Zidovudine	EBOV
PMID: 26752302	Preclinical	293 T cells	Interferon alpha	Interferon beta	EBOV
PMID: 26752302	Preclinical	293 T cells	Interferon alpha	Toremifene	EBOV
PMID: 1328433	Preclinical	FL cells	Interferon alpha	Ribavirin	HEV-B
PMID: 9722931	Preclinical	HEPG2 Cells	Interferon alpha	Thymosin alpha 1	HBV
PMID: 29753657	Preclinical	HG23 cells	Interferon alpha	Interferon gamma	NoV
PMID: 29890736	Preclinical	Huh7	Interferon alpha	Ribavirin	DENV
PMID: 24145541	Preclinical	Huh7	Interferon alpha	Ribavirin	HEV
PMID: 17855555	Preclinical	Huh7	Interferon alpha	Ribavirin	NoV
NCT00275938	2	Human	Interferon alpha	Ribavirin	HBV
NCT00114361	3	Human	Interferon alpha	Ribavirin	HBV
PMID: 15728914	0/1	Human	Interferon alpha	Ribavirin	HBV
PMID: 17470380	2	Human	Interferon alpha	Ribavirin	HCV
NCT00656006	2	Human	Interferon alpha	Ribavirin	HCV
NCT01447394	3	Human	Interferon alpha	Ribavirin	HCV
NCT00255034	4	Human	Interferon alpha	Ribavirin	HCV
NCT00383864	4	Human	Interferon	Ribavirin	HC

			alpha		V
NCT01045278;NCT00383864;NCT00255034;NCT01447394;PMID: 17470380;NCT00656006	4	Human	Interferon alpha	Ribavirin	HCV
PMID: 16984502	0/1	Human	Interferon alpha	ribavirin	HCV
PMID: 24661930	0/1	Human	Interferon alpha	Ribavirin	HPV
PMID: 24831606	0/1	Human	Interferon alpha	Ribavirin	MERS-CoV
PMID: 25278221	0/1	Human	Interferon alpha	Ribavirin	MERS-CoV
PMID: 33515771	0/1	Human	Interferon alpha	ribavirin	SARS-CoV-2
PMID: 34048876;ChiCTR2000029387	0/1	Human	Interferon alpha	Ribavirin	SARS-CoV-2
PMID: 32765274	0/1	Human	Interferon alpha	Ribavirin	SARS-CoV-2
NCT00140725	3	Human	Interferon alpha	Lamivudine	HBV
NCT02598063	4	Human	Interferon alpha	Lamivudine	HBV
PMID: 16677149	2	Human	Interferon alpha	Lamivudine	HDV
PMID: 30187599;NCT01706575	2	Human	Interferon alpha	Tenofovir	HBV
NCT01727271	4	Human	Interferon alpha	Tenofovir	HBV

NCT00000967	1	Human	Interferon alpha	Zidovudine	HIV
ChiCTR2000030535	0/1	Human	Interferon alpha	Lopinavir	SARS-CoV-2
NCT02637999	2	Human	Interferon alpha	Myrcludex B	HBV
NCT00418054	2	Human	Interferon alpha	Nitazoxanide	HCV
NCT01146535	2	Human	Interferon alpha	Oseltamivir	FLUAV
NCT02233075	2	Human	Interferon alpha	REP 2139	HBV
PMID: 33407619;NCT03546530	2	Human	Interferon alpha	Resveratrol	HBV
PMID: 17470380	2	Human	Interferon alpha	Taribavirin	HCV
NCT00118768	2	Human	Interferon alpha	Valopicitabine	HCV
PMID: 6329083	Preclinical	Human embryonic fibroblasts	Interferon alpha	Vidarabine	VZV
PMID: 24013700	Preclinical	Macaques	Interferon alpha	Ribavirin	MERS-CoV
PMID: 12821481	Preclinical	MDCK	Interferon alpha	Ribavirin	YFV
PMID: 3929044	Preclinical	African green monkeys	Interferon alpha	Interferon gamma	HSV-1
PMID: 15809077	Preclinical	OR6 cells	Interferon alpha	mizoribine	HCV

PMID: 31362004	Preclinical	PLC/PRF/5	Interferon alpha	Sofosbuvir	HEV
PMID: 2987369	Preclinical	Unknown	Interferon alpha	Vidarabine	HSV-1
PMID: 2987369	Preclinical	Unknown	Interferon alpha	Vidarabine	HSV-2
PMID: 23274666	Preclinical	Unknown	Interferon alpha	Interferon lambda	HCV
PMID: 21255610;PMID: 16940091	Preclinical	Unknown	Interferon alpha	NIM811	HCV
PMID: 6100083	Preclinical	Unknown	Interferon alpha	Prostaglandin D2	HSV-1
PMID: 1318909	Preclinical	Unknown	Interferon alpha	Trifluridine	HSV-1
PMID: 27496974	Preclinical	Vero	Interferon alpha	Ribavirin	CHIKV
PMID: 23594967	Preclinical	Vero	Interferon alpha	Ribavirin	MERS-CoV
PMID: 15288617	Preclinical	Vero	Interferon alpha	Ribavirin	SARS-CoV
PMID: 26527529	Preclinical	Vero	Interferon alpha	Ribavirin	SFTSV
PMID: 12821481	Preclinical	Vero	Interferon alpha	Ribavirin	YFV
PMID: 29109164	Preclinical	Vero	Interferon alpha	Ribavirin	ZIKV
PMID: 17101321	Preclinical	Vero	Interferon alpha	Mycophenolic acid	HCV
PMID: 21536800	Preclinical	Vero	Interferon alpha	Rupintrivir	EV-A71
PMID: 1331251	Preclinical	Vero cells	Interferon alpha	Interferon gamma	HSV-1
PMID: 16772029	Preclinical	Vero cells	Interferon alpha	Interferon gamma	HSV-2

PMID: 17191018	Preclinical	Vero cells	Interferon alpha	Interferon gamma	SARS-CoV
PMID: 12525074	Preclinical	WISH; Vero cells	Interferon alpha	Shuanghuanglian	HEV-B
PMID: 26752302	Preclinical	293 T cells	Interferon beta	Zidovudine	EBOV
PMID: 26752302	Preclinical	293 T cells	Interferon beta	Lamivudine	EBOV
PMID: 26752302	Preclinical	293 T cells	Interferon beta	Tenofovir	EBOV
PMID: 26752302	Preclinical	293 T cells	Interferon beta	Toremifene	EBOV
PMID: 25245230	Preclinical	A549; Calu-3	Interferon beta	Interferon lambda	FLUAV
PMID: 31924756	Preclinical	Calu-3	Interferon beta	Remdesivir	MERS-CoV
PMID: 18057251	Preclinical	FB	Interferon beta	Interferon gamma	HSV-1
PMID: 1328409	Preclinical	HMF	Interferon beta	Interferon gamma	HEV-B
NCT00249860	3	Human	Interferon beta	Ribavirin	HCV
NCT00002238	3	Human	Interferon beta	Zidovudine	HIV
PMID: 25462341	Preclinical	Mice	Interferon beta	Ribavirin	VSV
PMID: 19906941	Preclinical	Mice	Interferon beta	Interferon gamma	HSV-1
PMID: 31362004	Preclinical	PLC/PRF/5	Interferon beta	Sofosbuvir	HEV
PMID: 15604425	Preclinical	Unknown	Interferon beta	Interferon gamma	VZV
PMID: 15288617	Precli	Vero	Interferon	Ribavirin	SAR

	nical		beta		S-CoV
PMID: 26527529	Preclinical	Vero	Interferon beta	Ribavirin	SFTSV
PMID: 24096239	Preclinical	Vero	Interferon beta	Mycophenolic acid	MERS-CoV
PMID: 16099899;PMID: 12388715	Preclinical	Vero cells	Interferon beta	Interferon gamma	HSV-1
PMID: 17191018	Preclinical	Vero cells	Interferon beta	Interferon gamma	SARS-CoV
PMID: 8250541	Preclinical	HEp-2	Interferon gamma	TNF-alpha	HSV-1
PMID: 8250541	Preclinical	HEp-2	Interferon gamma	TNF-alpha	HSV-2
PMID: 29753657	Preclinical	HG23 cells	Interferon gamma	Interferon lambda	NoV
PMID: 31362004	Preclinical	PLC/PRF/5	Interferon gamma	Sofosbuvir	HEV
PMID: 26527529	Preclinical	Vero	Interferon gamma	Ribavirin	SFTSV
PMID: 16860835	Preclinical	Vero cells	Interferon gamma	Interleukin 4	SARS-CoV
ChiCTR2000030262	0/1	Human	Interferon kappa	TFF2	SARS-CoV-2
NCT00097045	2	Human	Interferon omega	Ribavirin	HCV
PMID: 25624323	Preclinical	Huh7	INX-08189	Ribavirin	DENV
NCT01425970	2	Human	INX-08189	Ribavirin	HCV
PMID: 27353263	Precli	RD	Itraconazole	Suramin	EV-

	nical				A71
PMID: 27353263	Preclinical	RD	Itraconazole	Rupintrivir	EV-A71
NCT03416491	2	Human	KW-136	Sofosbuvir	HCV
PMID: 22214282	2	Human	Lactic acid	Salicylic acid	MCV
PMID: 26752302	Preclinical	293 T cells	Lamivudine	Tenofovir	EBOV
PMID: 26752302	Preclinical	293 T cells	Lamivudine	Zidovudine	EBOV
PMID: 26752302	Preclinical	293 T cells	Lamivudine	Toremifene	EBOV
PMID: 19374144	Preclinical	AD38	Lamivudine	Tenofovir	HBV
NCT02181933	3	Human	Lamivudine	Zidovudine	HIV
NCT03223402	0/1	Human	Lamivudine	Nevirapine	HIV
NCT02202473	4	Human	Lamivudine	Oxymatrine	HBV
NCT00002371	3	Human	Lamivudine	Stavudine	HIV
NCT00124241	2	Human	Lamivudine	Telbivudine	HBV
PMID: 8721544	Preclinical	MDCK	lamivudine	Penciclovir	HBV
PMID: 25523147	Preclinical	MDCK	Laninamivir	Pyruvaldehyde	FLUAV
PMID: 25523147	Preclinical	MDCK cells	Laninamivir	Pyruvaldehyde	FLUAV
PMID: 28882564	Preclinical	GT1a	Ledipasvir	Sofosbuvir	HCV
PMID: 28882564	Preclinical	GT1a	Ledipasvir	Radalbuvir	HCV
PMID: 28882564	Preclinical	GT1a	Ledipasvir	Vedroprevir	HCV
PMID: 28882564	Preclinical	GT1a/b cell	Ledipasvir	Radalbuvir	HCV

		lines			
PMID: 28882564	Preclinical	GT1a/b cell lines	Ledipasvir	Vedroprevir	HCV
PMID: 31594756	Preclinical	Huh7	Ledipasvir	Sofosbuvir	YFV
PMID: 27348483	2	Human	Ledipasvir	sofosbuvir	HCV
PMID: 32531259	2	Human	ledipasvir	Sofosbuvir	HCV
NCT02472886	3	Human	Ledipasvir	Sofosbuvir	HCV
PMID: 29637511	3	Human	ledipasvir	sofosbuvir	HCV
NCT02480166	4	Human	Ledipasvir	Sofosbuvir	HCV
PMID: 26196665	3	Human	Ledipasvir	Sofosbuvir	HIV-1
PMID: 21079551	Preclinical	HPTC	Leflunomide	Sirolimus	BKV
PMID: 30040968	Preclinical	ARPEp	Letermovir	Maribavir	CMV
PMID: 22856583	Preclinical	Unknown	Levulinic acid	Sodium dodecyl sulfate	NoV
PMID: 25412347	Preclinical	Vero	LiCl	Teriflunomide	EV-A71
ChiCTR2000029573	0/1	Human	Litonavir	Lopinavir	SARS-CoV-2
NCT02430181	2	Human	Lonafarnib	Ritonavir	HDV
PMID: 29950446	Preclinical	Mice	Lonafarnib	Myrcludex B	HDV
PMID: 26198719	Precli	Commo	Lopinavir	Ritonavir	ME

	nical	n marmoset			RS-CoV
NCT00648999	4	Human	Lopinavir	Ritonavir	HIV
ISRCTN Registry 48776874	0/1	Human	Lopinavir	Ritonavir	HPV
ChiCTR2000029308	4	Human	Lopinavir	Ritonavir	SARS-CoV-2
PMID: 32759267	Preclinical	Vero	lopinavir	Ritonavir	SARS-CoV-2
PMID: 33333292	Preclinical	Vero	Lopinavir	Nitazoxanide	SARS-CoV-2
PMID: 33333292	Preclinical	Vero	Lopinavir	Umifenovir	SARS-CoV-2
PMID: 22359863	Preclinical	SPEV cells	Luromarin	Meglumine acetrizoate	TBEV
PMID: 30040968	Preclinical	ARPEp	Maribavir	Sirolimus	CMV
PMID: 24070820	Preclinical	MRC-5	maribavir	S3i-201	CMV
PMID: 30150460;NCT02603952	2	Human	MEDI8852	Oseltamivir	FLUAV
PMID: 26794398	Preclinical	Mice	Mefenamic acid	Ribavirin	CHIKV
PMID: 32194980	Preclinical	In-silico	Melatonin	Mercaptopurine	SARS-CoV-2

PMID: 25542975	Preclinical	N/A	Mercaptopurine	Mycophenolic acid	MERS-CoV
PMID: 29126899	Preclinical	Vero	Merimepodib	Ribavirin	JUNV
PMID: 29126899	Preclinical	Vero	Merimepodib	Ribavirin	LASV
PMID: 29126899	Preclinical	Vero	Merimepodib	Ribavirin	ZIKV
PMID: 26022200	Preclinical	MDCK	MI-701	oseltamivir	FLUAV
PMID: 27565991	Preclinical	Vero cells	miRNA	miRNA	CHIKV
PMID: 6249191	Preclinical	RK-13; Vero	MMUdR	Phosphonoacetic Acid	HSV-1
PMID: 28807916	Preclinical	HG23	Mycophenolic acid	Ribavirin	NoV
PMID: 28807916	Preclinical	HG23	Mycophenolic acid	Tacrolimus	NoV
PMID: 24582714	Preclinical	Huh7	Mycophenolic acid	Ribavirin	HEV
PMID: 25542975	Preclinical	N/A	Mycophenolic acid	Tioguanine	MERS-CoV
NCT03546621	2	Human	Myrcludex B	Tenofovir	HBV
NCT00002381	1	Human	Nelfinavir	Nevirapine	HIV
PMID: 11907486;NCT00000913	2	Human	Nelfinavir	Saquinavir	HIV
PMID: 30104275	Preclinical	Huh7	Nitazoxanide	Ribavirin	NoV
NCT01610245	3	Human	Nitazoxanide	Oseltamivir	FLUAV
NCT01610245	3	Human	Nitazoxanide	Oseltamivir	FLUBV
PMID: 25451059	Preclinical	MDCK	Nitazoxanide	Oseltamivir	FLUAV

PMID: 25451059	Preclinical	MDCK	Nitazoxanide	Zanamivir	FLUAV
PMID: 33333292	Preclinical	Vero	Nitazoxanide	Remdesivir	SARS-CoV-2
PMID: 33333292	Preclinical	Vero	Nitazoxanide	Umifenovir	SARS-CoV-2
PMID: 26225754	Preclinical	Mice	NITD008	Vorinostat	WNV
PMID: 28063993	Preclinical	RD; Vero; HEK-293T	NITD008	NK-1.9k	EV-A71
PMID: 28049006	Preclinical	RPE	Obatoclax	Saliphenylhalamide	ZIKV
PMID: 23523553	Preclinical	A549	Oseltamivir	PD-0325901	FLUAV
PMID: 23523553	Preclinical	A549	Oseltamivir	Refametinib	FLUAV
PMID: 23523553	Preclinical	A549	Oseltamivir	Selumetinib	FLUAV
PMID: 30428049;NCT02342249	2	Human	Oseltamivir	Pimodivir	FLUAV
NCT04261270	3	Human	Oseltamivir	Ritonavir	SARS-CoV-2
PMID: 19273672	Preclinical	MDCK	Oseltamivir	ribavirin	FLUAV
PMID: 20633577	Preclinical	MDCK	Oseltamivir	Peramivir	FLUAV
PMID: 25547360	Preclinical	MDCK	Oseltamivir	Pimodivir	FLUAV

PMID: 19586764	Preclinical	MDCK	Oseltamivir	Pomegranate	FLUAV
PMID: 25523147	Preclinical	MDCK	Oseltamivir	Pyruvaldehyde	FLUAV
PMID: 29079337	Preclinical	MDCK	Oseltamivir	Zanamivir	FLUAV
PMID: 29066417	Preclinical	Mice	Oseltamivir	PUL-042	FLUAV
PMID: 29066417	Preclinical	Mice	Oseltamivir	PUL-042	FLUBV
PMID: 17066897	Preclinical	Mice	Oseltamivir	Ribavirin	FLUAV
PMID: 18725448	Preclinical	Mice	Oseltamivir	Ribavirin	FLUAV
PMID: 17066897	Preclinical	Mice	Oseltamivir	Ribavirin	FLUBV
PMID: 22145356	Preclinical	Mice	Oseltamivir	Ridostin	FLUAV
PMID: 22617756;PMID: 17176629	Preclinical	Mice	Oseltamivir	Rimantadine	FLUAV
PMID: 25274854	Preclinical	Mice	Oseltamivir	Simvastatin	FLUAV
PMID: 29652799	Preclinical	H2.37	PD0325901	rapamycin	RVFV
NCT00001997	0/1	Human	PEG IL-2	Zidovudine	HIV
PMID: 18983873	Preclinical	Hela cells	Peptide	Peptide	SARS-CoV
PMID: 25523147	Preclinical	MDCK	Peramivir	Pyruvaldehyde	FLUAV
PMID: 25523147	Preclinical	MDCK cells	Peramivir	Pyruvaldehyde	FLUAV
PMID: 20943201;PMID: 15561867	Preclinical	Mice	Peramivir	Rimantadine	FLUAV
PMID: 12011541	Preclinical	Unknown	Peramivir	Ribavirin	FLUAV

PMID: 25547360	Preclinical	MDCK	Pimodivir	Zanamivir	FLUAV
ChiCTR2000030218	0/1	Human	Pinavir	Ritonavir	SARS-CoV-2
PMID: 21565949	0/1	Human	Plasma	Ribavirin	CCHFV
PMID: 3662477	Preclinical	Mice	poly(ICLC)	Ribavirin	RVFV
PMID: 25523147	Preclinical	MDCK	Pyruvaldehyde	Zanamivir	FLUAV
PMID: 28882564	Preclinical	GT1a	Radalbuvir	Sofosbuvir	HCV
PMID: 28882564	Preclinical	GT1a	Radalbuvir	Vedroprevir	HCV
PMID: 28882564	Preclinical	GT1a/b cell lines	Radalbuvir	Vedroprevir	HCV
PMID: 24262278;NCT01260350	2	Human	Radalbuvir	Sofosbuvir	HCV
PMID: 26374952	Preclinical	Mice	Rapamycin	Valacyclovir	HIV-1
PMID: 15168801	Preclinical	HEp-2	RBI034	Ribavirin	RSV
PMID: 33333292	Preclinical	Vero	Remdesivir	Umifenovir	SARS-CoV-2
PMID: 27257978;NCT02646189	2	Human	REP 2139-Ca	thymosin alpha 1	HBV
PMID: 26408347	Preclinical	HEV3	Ribavirin	Sofosbuvir	HEV
PMID: 28807916	Preclinical	HG23	Ribavirin	Tacrolimus	NoV

PMID: 30036559	Preclinical	Huh7	Ribavirin	Silvestrol	HEV
PMID: 30104275	Preclinical	Huh7	Ribavirin	Tizoxanide	NoV
PMID: 32531259	2	Human	ribavirin	Sofosbuvir	HCV
NCT03069001	4	Human	Ribavirin	Sofosbuvir	HCV
NCT01871662	3	Human	Ribavirin	Silibinin	HCV
NCT01726946	2	Human	Ribavirin	VX-135	HCV
https://journals.sagepub.com/doi/pdf/10.1177/095632029500600205	Preclinical	MDCK	Ribavirin	Zanamivir	FLUAV
PMID: 3729336	Preclinical	MDCK	Ribavirin	Selenazofurin	FLUAV
PMID: 3729336	Preclinical	MDCK	Ribavirin	Selenazofurin	FLUBV
PMID: 7447417	Preclinical	MDCK	Ribavirin	Rimantadine	FLUAV
PMID: 31362004	Preclinical	PLC/PRF/5	Ribavirin	Sofosbuvir	HEV
PMID: 21466823	Preclinical	Unknown	Ribavirin	Rupintrivir	EV-A71
PMID: 21466823	Preclinical	Unknown	Ribavirin	Rupintrivir	HRV-B14
PMID: 21466823	Preclinical	Unknown	Ribavirin	Rupintrivir	PV
PMID: 29315647	Preclinical	Vero	Ribavirin	Teriflunomide	JUNV
PMID: 7434742	Preclinical	chick embryo fibroblast	Ribavirin	Rimantadine	SINV
PMID: 3445584	Precli	Unkno	Rimantadine	Selenious acid	FLU

	nical	wn			AV
PMID: 17898705 ;NCT00000913	2	Human	Ritonavir	Saquinavir	HIV
NCT00440271	3	Human	ritonavir	Tipranavir	HIV
PMID: 27353263	Preclinical	RD	Rupintrivir	Suramin	EV-A71
PMID: 31108015;NCT02956629	2	Human	Ruzasvir	Uprifosbuvir	HCV
PMID: 10682127;NCT00002333	2	Human	Saquinavir	Zalcitabine	HIV
PMID: 6151377	Preclinical	Vero-76; Vero-E6; LLC-MK2 cells	Selenazofurin	Tiazofurin	YFV
PMID: 6151377	Preclinical	Vero-76; Vero-E6; LLC-MK2 cells	Selenazole-4-carboxyamide-adenine dinucleotide	Tiazofurin	JEV
PMID: 33801811	Preclinical	Huh7	Sertraline	Toremifene	EBOV
NCT02168361	4	Human	Simeprevir	Sofosbuvir	HCV
NCT03069001	4	Human	Simeprevir	Sofosbuvir	HCV
NCT00994773	1	Human	Simvastatin	Tenofovir	HBV
PMID: 28882564	Preclinical	GT1a	Sofosbuvir	Vedroprevir	HCV
PMID: 27035622	Preclinical	Huh7	Sofosbuvir	Telaprevir	HCV
PMID: 26571066;NCT02201940	3	Human	Sofosbuvir	Velpatasvir	HCV

PMID: 30203225	3	Human	sofosbuvir	velpatasvir	HCV
PMID: 24704033	Preclinical	Piglet	Sophora flavescens extract	Stevioside	RoV
NCT00002109	3	Human	Stavudine	Timunox	HIV
PMID: 27053240	Preclinical	LLC-MK2	Suramin	Zanamivir	hPIV-3
PMID: 26036224	Preclinical	Huh 9-13; HuH6; Huh 5-2 cells	Tegobuvir	Telaprevir	HCV
PMID: 19374144	Preclinical	AD38	Telbivudine	Tenofovir	HBV
NCT00805675;PMID: 30601336	3	Human	Telbivudine	Tenofovir	HBV
NCT00128544	2	Human	Telbivudine	Valtorcitabine	HBV
PMID: 26752302	Preclinical	293 T cells	Tenofovir	Toremifene	EBOV
PMID: 26752302	Preclinical	293 T cells	Tenofovir	Zidovudine	EBOV
PMID: 29851204;NCT02579382	2	Human	Tenofovir	Vesatolimod	HBV
NCT00002109	3	Human	Timunox	Zidovudine	HIV
PMID: 26752302	Preclinical	293 T cells	Toremifene	Zidovudine	EBOV
PMID: 21487108	2	Human	Valganciclovir	Zidovudine	KSHV
NCT00002081	0/1	Human	Zalcitabine	Zidovudine	HIV

Vegard Myhre

NTNU

Kunnskap for en bedre verden