HLA|COVID-19 Database Access Manual

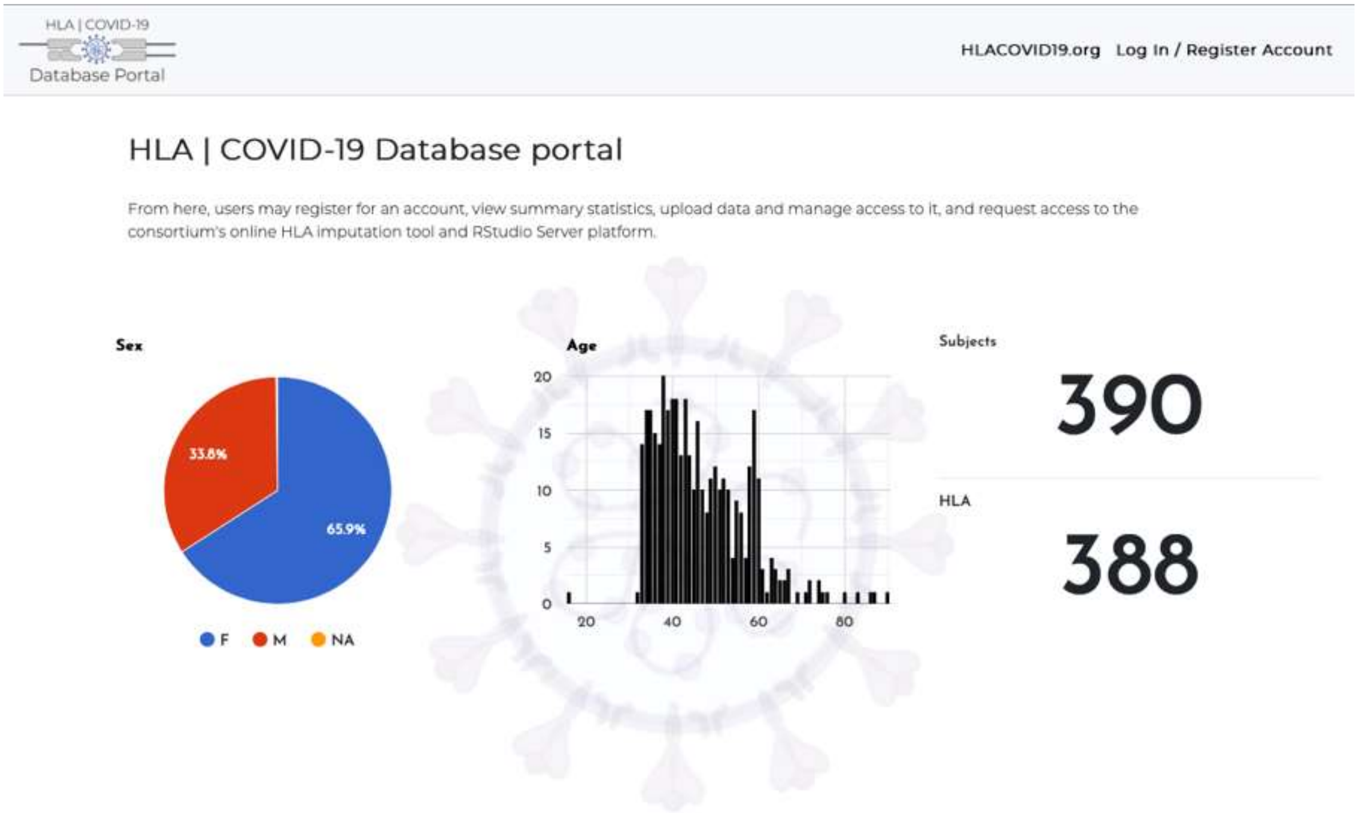
V1.0 October 26, 2020

Contents

1. Location

The HLA|COVID-19 Database (HCDB) is online at https://database-hlacovid19.org, and can be accessed via any modern browser.

The database landing page is shown below (Figure 1). This page displays summary statistics regarding currently loaded subject data in the main part of the page, and includes links to the HLA|COVID-19 web page and other database-related links at the top.



HLA | COVID-19 Database portal

From here, users may register for an account, view summary statistics, upload data and manage access to it, and request access to the consortium's online HLA imputation tool and RStudio Server platform.

Figure 1. Database Landing Page

2. Access

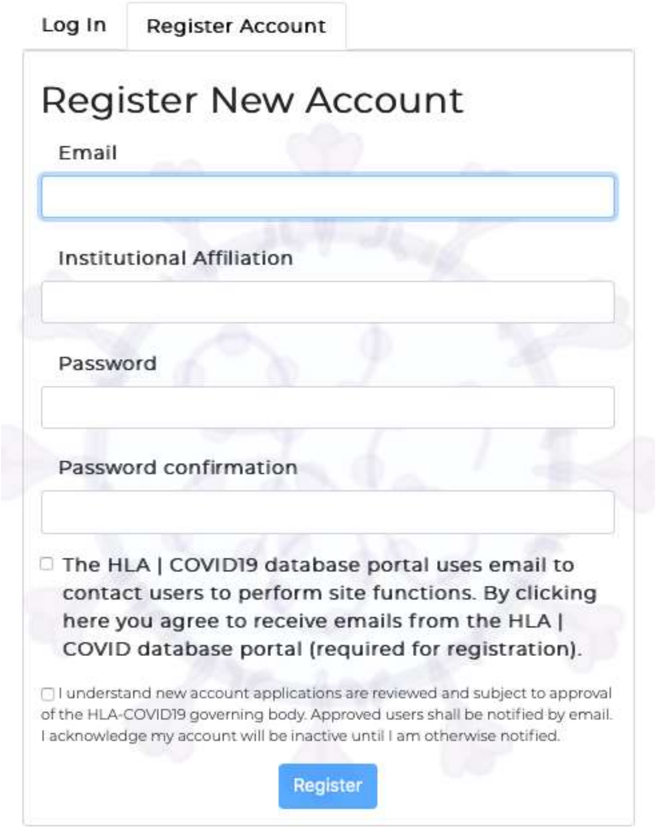
2.A Registering an Account

All HCDB users must have database accounts. To register for a HCDB account, click ***Log In / Register Account*** in the navigation bar at the top of the landing page, and then click ***Register Account*** on the resulting page (Figure 2).

Figure 2. Log In/Register Account Page

On the resulting page (Figure 3), enter your email address, institutional affiliation and your account password (twice). Your email address will be the primary means of identifying your account.

Check each box at the bottom of the page, agreeing to receive emails from the HCDB and acknowledging that new account applications are subject to the approval of the HLA-COVID19 governing body. Click **Register**.



☐ The HLA | COVID19 database portal uses email to contact users to perform site functions. By clicking here you agree to receive emails from the HLA | COVID database portal (required for registration).

☐ I understand new account applications are reviewed and subject to approval of the HLA-COVID19 governing body. Approved users shall be notified by email. I acknowledge my account will be inactive until I am otherwise notified.

Figure 3. Register New Account Page

2.B Logging into the HCDB

Click ***Log In*** tab on click the ***Log In / Register Account*** page (Figure 2), and then enter the email address and password that you used to create your account (See section 2.A).

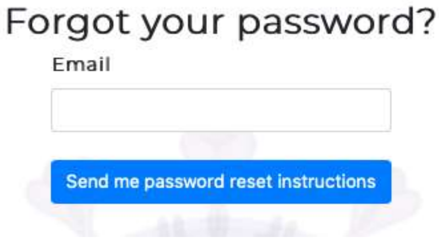
The navigation bar at the top of the page will include new links, depending on the selections that you made when you created your account.

- ***HLACOIVD19.org*** will lead to the hlacovid19.org website's landing page.
- ***File Uploads*** will lead to your **File Upload History** page.
- ***RStudio Server*** will open a new tab in which you can log into the RStudio cloud server.
- ***My Project*** will lead to the project-data management pages if you have uploaded a data file.
- ***My Account*** will lead to the **Your Account** account management page (Figure 5).
- ***Logout*** will log you out of the HCDB.

These options are described in detail section 3, below.

2.C Resetting your Password

If you cannot remember your password, click ***Forgot your password?*** at the bottom of the ***Log In*** tab. On the next page (Figure 4), enter the email address that you used to create your account (See section 2.A), and click **Send me password reset instructions**.



Forgot your password?

Email

Figure 4. Password Reset

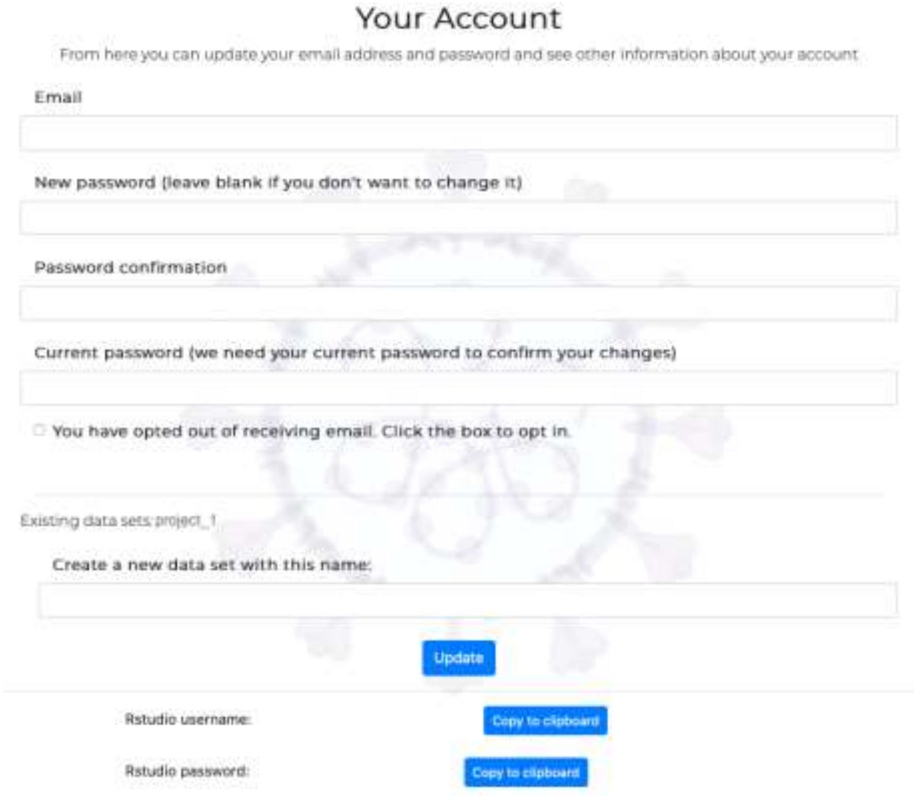
You will be taken to the ***Retry Log in*** page. Instructions on resetting your password will be sent to your email address. Follow those instructions to create a new password, and then enter the email address that you used to create your account and your new password on the ***Retry Log*** in page. Your password will not be changed until you follow the instructions in the email and create a new one.

3. HCDB Functions

3.A **Your Account** page

On the **Your Account** page (Figure 5), you can update your email address and password and enter project names for new data sets. In addition, your RStudio cloud server username and password will be shown at the bottom of the page.

Any Project Names you have registered will be listed in the ***Existing data sets*** section. A project named '*project_1*' is shown in Figure 5.



Your Account

From here you can update your email address and password and see other information about your account

Email

New password (leave blank if you don't want to change it)

Password confirmation

Current password (we need your current password to confirm your changes)

☐ You have opted out of receiving email. Click the box to opt in.

Existing data sets: project_1

Create a new data set with this name:

Rstudio username:

Rstudio password:

Figure 5. MyAccount Page

To change your email, enter a new email address in the ***Email*** field, enter your password in the ***Password confirmation*** field, and click **Update**.

To change your password, enter a new password in the ***New password*** field, enter your current password in the ***Password confirmation*** field, and click **Update**.

If you are an original HCDB user, there may be an empty checkbox below the ***Current password*** field, followed by a message that reads, "You have opted out of receiving email. Click the box to opt in." (Figure 5). In these cases, please check this box, enter your password in the ***Current password*** field, and click **Update**. This will ensure that that you can receive HCDB-related emails.

If you opted in to receiving emails when you registered your HCDB account, you will instead see a message that reads, “You have opted into receiving email from the database portal. Click the box to opt out. Warning: opting out of email may render some website features unusable.”

To create a dataset, provide a project name for the associated data in the ***Create a new dataset with this name*** field. This exact Project Name must be associated with all subject data loaded into the HCDB for this project. To avoid confusion between datasets each Project Name should be:

- Descriptive
- Specific to the dataset
- Potentially unique

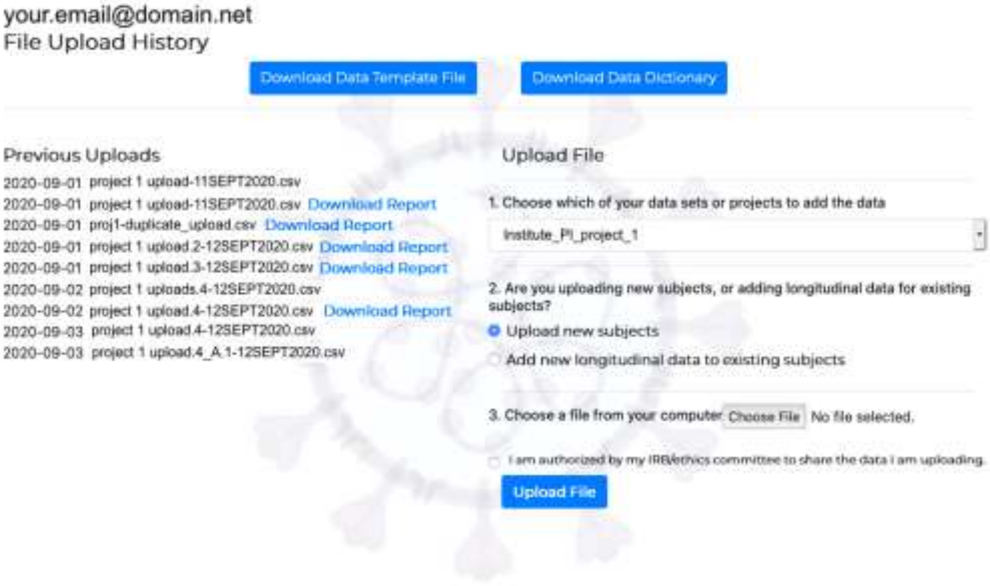
Project names can be up to 100 characters in length. Structure your Project Name as ***institution-name_investigator-name_cohort-description***. Once you have entered a new Project Name in the ***Create a new dataset with this name*** field, enter your password.

You can create as many datasets as necessary.

You can copy your RStudio cloud server username or password to the clipboard by clicking **Copy to clipboard**.

3.B **File Uploads** page

On the **File Uploads** page (Figure 6), you can download the data-template for data submission and the data dictionary. This page presents a record of all of your previous file-uploads, and provides links to download reports for each uploaded file that was processed by the database.



your.email@domain.net

File Upload History

Previous Uploads

2020-09-01 project 1 upload-11SEPT2020.csv
2020-09-01 project 1 upload-11SEPT2020.csv Download Report
2020-09-01 proj1-duplicate_upload.csv Download Report
2020-09-01 project 1 upload.2-12SEPT2020.csv Download Report
2020-09-01 project 1 upload.3-12SEPT2020.csv Download Report
2020-09-02 project 1 uploads.4-12SEPT2020.csv
2020-09-02 project 1 upload.4-12SEPT2020.csv Download Report
2020-09-03 project 1 upload.4-12SEPT2020.csv
2020-09-03 project 1 upload.4_A.1-12SEPT2020.csv

Upload File

1. Choose which of your data sets or projects to add the data

Institute_PI_project_1

2. Are you uploading new subjects, or adding longitudinal data for existing subjects?

● Upload new subjects
○ Add new longitudinal data to existing subjects

3. Choose a file from your computer Choose File No file selected.

☐ I am authorized by my IRB/ethics committee to share the data I am uploading.

Figure 6. File Uploads Page

Click the **Download Data Template File** to download a copy of the UploadTemplate.csv file. This is a comma-separated value (CSV) file that includes all of the HCDB fields separated by commas (Figure 7). This file should be opened in a spreadsheet application, and the HCDB fields will appear as column-headers. **DO NOT EDIT ANY OF THESE FIELD NAMES. DO NOT ADD ANY FIELD NAMES**. Data for each subject should be entered on a single line of the spreadsheet. Once all of the data have been entered, the file should be saved as a CSV file.

origin_identifier	project_name	country_of_residence	sex	gender	education	age	ancestry	race	ethnicity	pregnant	height_cm	weight_kg	drb1_1	drb1_2	dqb1_1	dqb1_2	dpb1_1	dpb1_2	a_1	a_2	b_

Figure 7. Data Upload Template

Click **Download Data Dictionary** to download a copy of the HLA_COVID19_data_dictionary.xlsx file. This is an MS Excel file that identifies all the HCDB fields (in Column B, **column name**), organized by data-category (in Column A). The data-categories are:

- Subjects
- HLA
- COVID19 Symptoms
- Hospitalization
- Risk Factors
- Lab Tests
- Treatments
- Comorbidities

The type of data that should be entered for each field is shown in Column C (**data type**).

- If the data type is ‘boolean’, **only T (for TRUE) or F (for FALSE) values should be entered for that field**.
- If the data type is ‘number’, **only numerals (0 – 9) should be entered for that field**.
- If the data type is ‘decimal’, **only decimal numbers should be entered for that field**.
- If the data type is ‘text’, any characters can be entered for that field. However, the specifics of the text may be restricted by the instructions in the “notes” column (Column E).

Fields for which you have no data can be left blank, or can be submitted with NA values.

The values in the **required?** column (Column D) indicate if column data must be included with each upload, as described by instructions in the **notes** column.

Values for the **origin_identifier**, **project_name**, **country_of_residence**, **age**, **c19_test_result_positive** and **c19_test_type** fields **must** be provided for every subject.
Values for either **ancestry** alone or **race** and **ethnicity** together **are recommended** for every subject.

In general, the **race** and **ethnicity** fields should be reserved for data described using United States Office of Management and Budget classifications for Race and Ethnicity (https://grants.nih.gov/grants/guide/notice-files/not-od-15-089.html). This includes five racial categories (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White) and two ethnic categories (Hispanic or Latino, and Not Hispanic or Latino).

The **ancestry** field should be used for data described using other population or ancestry identifiers.

When HLA data are uploaded, it is strongly recommended that the reference_database (e.g., IPD-IMGT/HLA Database), reference_database_version (e.g., 3.41.0), typing_method_name, and typing_method_version information be provided for each subject when available.

3.B.1 **Uploading Data for New Subjects**

To upload data for new subjects, select the pertinent Project Name in the **Choose which of your data sets or projects to add the data** pull-down menu, click **Upload new subjects** and **Choose File**, and select the modified version of the UploadTemplate.csv file that includes your data. When you have selected a file, the filename will be displayed to the right of the Choose File button.

Please note that your institution's institutional review board (IRB) or ethics committee must approve the sharing of these data for research use. If you have received that approval, check the box that indicates that you are authorized by your IRB/ethics committee to share these data. *If you do not check this box, the data in your uploaded file will not be loaded into the HCDB.*

Once you have selected the file for upload, click **Upload File**.

NOTE: A given filename can only be uploaded once. An attempt to load a duplicate filename will result in an alert box containing an error message.

When a file has been successfully uploaded, a ***Download Report*** (Figure 8) link will be displayed to the right of the filename in the Previous Uploads section of the page. You may have to refresh the page to update the Previous Uploads section. Click that link to download a text file that identifies the user who uploaded the data, the name of the file uploaded, the Project Name associated with the uploaded data, the time and type of upload, the number of subjects uploaded, and a list of any incorrect column headers.

```
User: your.email@domain.net
Filename: project 1 upload-11SEPT2020.csv
Project: Institute_PI_project_1
Data depositing approved by IRB/ethics board? true
Upload time: Sep 11, 2020 23:19
Upload type: new_subject
Number of subjects uploaded: 2
Incorrect column headers:  - (If list is not empty check
the data dictionary for correct variable names).
```

Figure 8. Example Download Report

If a file has not been successfully uploaded, no *Download Report* link will be displayed beside the file. In cases like these, check the file to make sure that the origin_identifiers for the subjects in the file have not been previously loaded for that Project Name, and that the correct Project Name is the project_name field. Non-longitudinal data (see section 3.B.2) for a subject under a given Project Name can only be loaded once.

If you have loaded incorrect column headers, the column headers will be listed to the right of “Incorrect column headers:” (e.g., ‘["patient_self_reported_positive"]’).

When you have uploaded data for a subject identifier with a specific origin_identifier, that subject is assigned a unique HCDB identifier (a hlac19_id), which will be included on all downloaded data tables (see section 3.C.1).

3.B.2 **Adding New Longitudinal Data for Existing Subjects**

The data for fields in the **COVID19 Symptoms**, **Hospitalization**, **Lab Tests**, **Treatments** and **Comorbidities** data-categories (Column A of the Data Dictionary) are longitudinal data and can be updated for subjects as necessary.

To upload new longitudinal data:

- Select the pertinent Project Name in the **Choose which of your data sets or projects to add the data** pull-down menu
- Click **Add new longitudinal data to existing subjects**
- Click **Choose File**
- Select the modified version of the UploadTemplate.csv file that contains new longitudinal data for specific subjects.

Note: Only subjects with new longitudinal data should be included in this file. In addition to the fields for the updated longitudinal data, only the origin_identifier and project_name fields should be completed for these subjects.

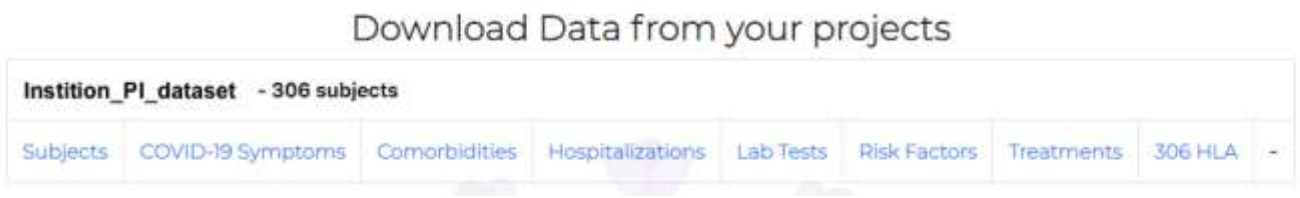
As described in section 3.B.1, only data that have been authorized by your IRB or ethics committee can be uploaded. Check the box that indicates that you are authorized by your IRB/ethics committee to share these data, and then click **Upload File**.

3.C Project-Data **Management** Pages

The ***My Project*** link will take you to a page with a Download Data tab and a Manage Access tab.

3.C.1 Download Data

The Download Data tab displays a set of links for the data-categories (section 3.B) in each of your projects and the projects to which you have access (section 3.C.2). Each Project Name will appear above a row boxes containing a link identifying each data-category (Figure 9). The number of subjects for that project will be to the right of the project name, and the number of subjects with HLA genotype data will be in the HLA box. When available, HLA genotyping quality metrics may appear in the box to the right of the HLA box. Click the link to download the CSV formatted data for each data-category in a given project. Each file includes each subject’s hlac19_id and origin_identifier.



Download Data from your projects

Instition_PI_dataset - 306 subjects

Figure 9. Download Data Tab

3.C.2 Manage Access

On the Manage Access tab, you can specify which HCDB users have access to the data you have uploaded for a specific Project Name. When you check the checkbox next to a specific HCDB user for a specific Project Name, that user will be authorized to download data from that Project Name.

4. RStudio Cloud Server

The RStudio cloud server supports the installation and development of data-management and -analysis tools. If you are not experienced with the R programming language and the RStudio IDE you **do not** need to use the RStudio cloud server. The RStudio cloud server can be accessed using the *RStudio server* link in in the navigation bar at the top of the page.

When you click that link, you will be taken to the **RStudio Sign In** page (Figure 10).

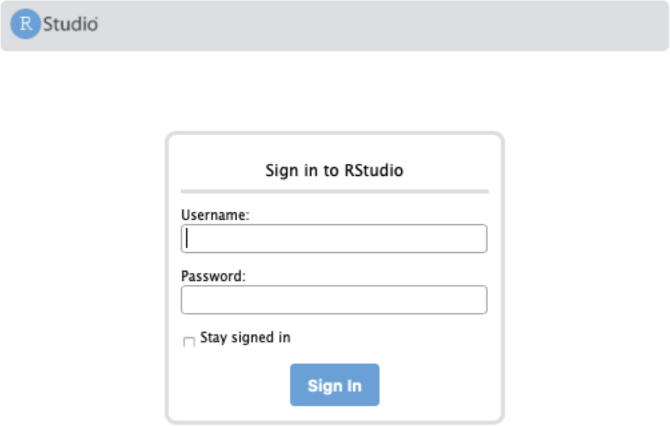


Figure 10. RStudio Server Page

4.A **Signing In to the R Studio Server**

To sign into the RStudio server, enter the **username** and **password** at the bottom of the **Your Account** page. You can copy the password to your clipboard by clicking **Copy to clipboard** (see section 3.A). If you want to remain signed into the RStudio server, check **Stay signed in**. Checking this box will allow you to return to your RStudio server environment, even after closing the window, by navigating to https://database-hlacovid19.org/rstudio/.

To **Sign out** of the RStudio server environment, click **Sign out** to the right of your username in the top right corner of the window (Figure 11).

Figure 11. RStudio Server Sign Out

4.B **RStudio Server Accounts**

Each RStudio server account is an independent installation of R version 4.02 in RStudio version 1.2.5042, with primarily default R packages installed. Each RStudio server user will have to install any additional R packages needed.

4.C **Shiny Server**

The database maintains a Shiny Server for hosting Shiny apps. Any outward facing data-analysis tools should be built into a Shiny app that can be hosted on the Shiny Server. Each RStudio Server account comes with shiny version 1.4.0.2 installed.

5 HLA Imputation Portal

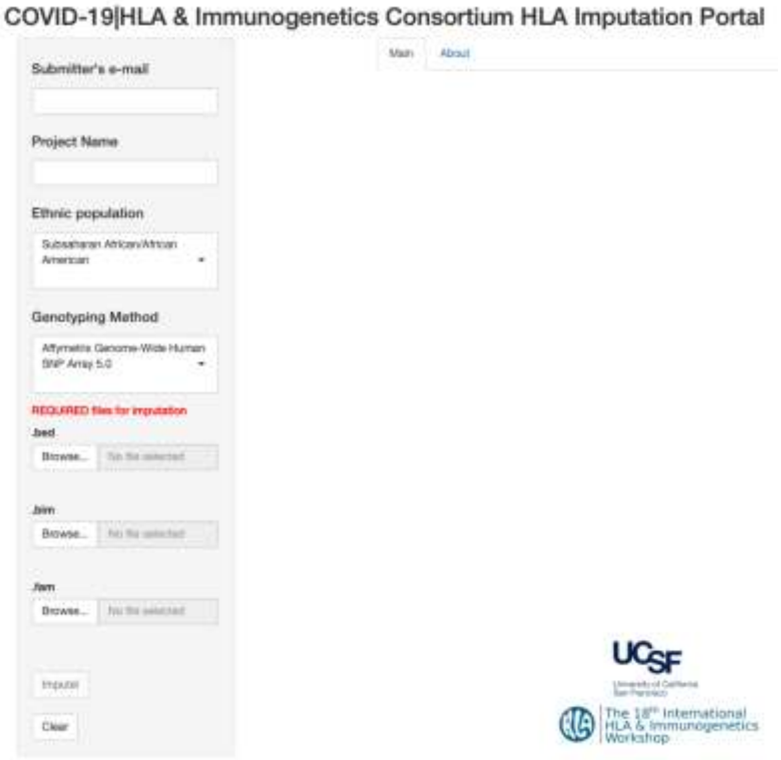
The HLA Imputation Portal (HIP) consumes .bed, .bim, and .fam files for SNP-genotyped subjects, and imputes HLA-A, -C, -B, -DRB1, -DQA1, -DQB1, and -DPB1 genotypes for each subject. The HIP does not consume .ped and .map files. PLINK can be used to convert .ped and .map files to .bed, .bim and .fam files on your system (zzz.bwh.harvard.edu/plink/data.shtml#bed).

Note: The HIP can only be applied to subjects with origin identifiers that have been previously loaded into the HCDB under a specific Project Name (see section 3.B.1).

SNPs must be described using hg19 SNP rs IDs and genomic coordinates. If your SNP data are not recorded using hg19 genome coordinates and annotations, lift-over tools are available online (e.g. https://genome.ucsc.edu/cgi-bin/hgLiftOver).

The HIP relies on 129 models built from genome-wide SNP data generated on 30 array platforms for subsets of African, Asian, European, Hispanic and Multi-ethnic groups. For details of the platforms and the associated population models, visit https://zhengxwen.github.io/HIBAG/platforms.html.

To access the HIP, go to https://database-hlacovid19.org/shiny in your browser, and click **HLA-Imputation-Portal/**. Once connected to the HIP, provide your HCDB account's associated **email address**, and the **Project Name** associated with the origin identifiers for each subject in your SNP dataset (Figure 12). As noted above, these origin identifiers **must** be included in the uploaded .fam file, and must have been loaded into the HCDB **before** using the HIP.



COVID-19|HLA & Immunogenetics Consortium HLA Imputation Portal

Submitter's e-mail

Project Name

Ethnic population: Subsaharan African/African American

Genotyping Method: Affymetrix Genome-Wide Human SNP Array 5.0

REQUIRED files for imputation

.bed: No file selected

.bim: No file selected

.fam: No file selected

Figure 12. HLA Imputation Portal

Select the pertinent population group in the **Ethnic population** pulldown menu, and the pertinent SNP genotyping assay in the **Genotyping Method** pulldown menu. Note that not all combinations of ethnic population and genotyping assay are possible. If a specific population group is not available for your genotyping assay, choose the **Multi-ethnic/Other** group.

Click **Browse…** for each of the .bed, .bim and .fam files to select the pertinent file for imputation. These data are extracted from your local files; the files are not uploaded to the HIP.

When the submitter's email and the Project Name have been provided, the population and assay have been selected, and the source files have been successfully uploaded, click **Impute!** to begin the imputation process. Any messages about the imputation process will be displayed in the HIP's Main tab. Specific information about these messages are provided in the About tab.

While the imputation is running, a circle of spinning dots will appear in the upper-right of the page, the HIP page will be greyed out, and a white bar with the message **Your imputation is running…** will appear near the top of the page.

When the imputation is complete, a message will appear in the Main tab, and an email notification will be sent to the address provided in the **Submitter's e-mail** field. Imputed HLA genotypes for each subject will be automatically loaded into the specified Project Name of the HCDB account associated with the Submitter's e-mail address for the origin identifiers in the .fam file. In addition, a downloadable file of posterior probability values for each subject and each locus will be loaded into your account.

5.A: **Recommendations for using the HIP**

Because the imputation process relies on specific ethnic models, it may be most efficient to generate separate .fam files for subjects of different ethnicities, and run each .fam file separately. Imputation performed using the Multi-ethnic models can take significantly longer than using the single-ethnicity models, and use of the African, Asian, European and Hispanic models when possible is recommended. In instances where a specific ethnic model is not available for a particular SNP assay, use the Multi-ethnic model.