Project Details	
Project Code	MRCIIAR26Br Mann
Title	Hidden codes: Genetic Determinants of HIV-1 Fitness and Immune Recognition.
Research Theme	IIAR
Project Type	Wet lab
Summary	This project addresses the ongoing challenge posed by HIV-1, a virus infecting approximately 38 million people globally, with Subtype C (C-HIV) as the most prevalent strain. Understanding why C-HIV has become predominant in certain regions of the world is crucial for deciphering its transmission dynamics and impact. Through advanced genetic analysis coupled with state-of-the-art immunological and virological experimental techniques, we aim to uncover the genetic determinants driving C-HIV’s success. This research will deepen our understanding of HIV-1 evolution and help develop innovative strategies to combat the virus and mitigate its impact.
Description	**Background:** HIV-1 remains a significant global health challenge, with approximately 38 million people infected worldwide. There are multiple subtypes of HIV-1, including A, B, C, D, and F, as well as numerous recombinant forms, each with distinct genetic variations that affect their transmission and pathogenicity. Among these, Subtype C (C-HIV) is the most prevalent, accounting for 46% of global infections. It is predominant in regions such as Southern Africa, India, and Ethiopia, where the healthcare infrastructure may be less developed, and access to antiretroviral therapy (ART) might be limited. Despite its regional concentration, the predominance of C-HIV raises critical questions about its potential evolutionary advantages in transmission, replication, and virulence. Gaining insights into the mechanisms behind the high prevalence of C-HIV is essential for a better understanding of the AIDS epidemic and for developing effective vaccines, therapies and cures. Within our 5-year funded MRC grant focusing on HIV-1 subtype B (B-HIV) transmission, we identified that transmitted/founder (T/F) viruses possess specific genetic sequences that are more prevalent than in non-transmitting variants. Building on this solid foundation, we aim to expand our understanding to a more global context by investigating non-subtype-B HIV (e.g. C-HIV and potentially A- and D-HIV). Key Research Question: How do specific genetic sequences within the HIV-1 genome influence the transmission efficiency and replicative fitness of non-subtype B virus and can this be used to compare viral fitness between subtypes? By investigating these genetic determinants, can we uncover potential evolutionary advantages that explains the global predominance of certain strains of HIV-1? **Specific Objectives:** 1) As seen previously with B-HIV, are the identified genetic sequences more prevalent in the viral genomes of non-subtype-B HIV T/F compared to non-subtype-B HIV viruses isolated at later stages of infection?

	2) Can transmission of non-subtype-B HIV viruses be modelled using a state-of-the-art ex vivo viral transmission assays that employs a mock viral quasi-species? 3) Does recoding the genetic sequence of the virus's genome, keeping the translated amino acid sequences unchanged, affect the transmission and replicative fitness of the viruses? 4) Are the genetic sequences linked to either transmission and/or replication fitness? Over the course of the studentship, the student will have the opportunity to take ownership and steer the project in several key areas: • Data Collection and Genomic Analysis: The student will lead the collection and analysis of viral genomic data, developing skills in bioinformatics and genomic sequencing. • In vitro and ex vivo Experiments: The student will design and conduct experiments to assess replicative fitness and transmission efficiency, gaining hands-on experience with various cell culture techniques and ex vivo human mucosal explant models. • Comparative Analysis and Hypothesis Testing: The student will compare findings within C-HIV strains and between different HIV subtypes (i.e. C-HIV vs B-HIV), formulating hypotheses and testing them to elucidate the genetic determinants of transmission and replication fitness. • Translation and Innovation: At every opportunity, the student will be encouraged to assess the impact of the research data how it can be exploited for further research opportunities. Moreover, the student will be encouraged to think about any commercial opportunities and potential clinical applications arising from the work. This project will equip the student with a comprehensive understanding of viral genomics, HIV transmission dynamics, replicative fitness as well as experience with using virological and immunological assays. The knowledge gained will contribute significantly to the broader field of HIV research and may inform future vaccine and therapeutic cure strategies. The student will be encouraged to explore alternate exploratory projects, fostering innovation and independent thinking in their research journey.
Supervisory Team	
Lead Supervisor	
Name	Dr Jamie Mann
Affiliation	Bristol
College/Faculty	Faculty of Health and Life Sciences
Department/School	Bristol Veterinary School
Email Address	jamie.mann@bristol.ac.uk
Co-Supervisor 1	
Name	Dr Katja Klein
Affiliation	Bristol
College/Faculty	Faculty of Health and Life Sciences
Department/School	Bristol Veterinary School
Co-Supervisor 2	
Name	Professor David Price
Affiliation	Cardiff

College/Faculty	Division of Infection and Immunity
Department/School	Cardiff University School of Medicine
Co-Supervisor 3	
Name	Dr Behroz Khan
Affiliation	Bristol
College/Faculty	Faculty of Health and Life Sciences
Department/School	Bristol Veterinary School