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HEALTH SYSTEM ANALYSIS OF THE BARRIERS TO ACCESS, AVAILABILITY, UTILISATION AND READINESS OF SEXUAL AND REPRODUCTIVE HEALTH SERVICES IN COVID-19 AFFECTED AREAS: DEVELOPMENT AND VALIDATION OF A DATA COLLECTION SYSTEM TO BE APPLIED FOR FUTURE HEALTH PANDEMICS

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SOMMARIO

Introduzione: La pandemia da Coronavirus 19 (COVID-19) ha fortemente influenzato l'erogazione dei servizi di salute sessuale, portando a gravi conseguenze in termini di salute individuale e pubblica. La raccolta dati in tempo reale è di primaria importanza al fine di monitorare l'impatto sull'erogazione e sull'accessibilità dei servizi in caso di future nuove emergenze sanitarie.

Obiettivi: Studio della durata di 3 anni, condotto nell'ambito di una più ampia collaborazione tra il Dipartimento di Ricerca Salute Sessuale e Riproduttiva dell'Organizzazione Mondiale della Sanità (OMS) e l'Università di Brighton (UOB) con l'Azienda Ospedaliera Universitaria Integrata di Verona (AOVR). L'obiettivo generale dello studio è quello di sviluppare e validare, attraverso la piattaforma REDCap (Research Electronic Data Capture), uno strumento elettronico di raccolta dati, sicuro e standardizzato, per la gestione di dati clinici inerenti a HIV ed infezioni a trasmissione sessuale (IST). Lo strumento ha lo scopo di gettare le basi per la costruzione di un'infrastruttura di ricerca volta a facilitare studi di implementazione multicentrici in grado di rispondere rapidamente a specifiche domande di ricerca al fine di informare e guidare processi decisionali.

Metodi: Lo sviluppo dello strumento si è avvalso di un approccio multidisciplinare (9 membri dello studio di AOVR e UOB con varia formazione), attraverso fasi distinte: *i)* identificazione di un set di variabili chiave standardizzate relate ad HIV-IST necessarie per aumentare la qualità degli studi osservazionali; *ii)* progettazione della struttura dello strumento secondo i principi chiave descritti in letteratura con particolare attenzione al concetto di modularità, flessibilità, intuitività, e conformità al regolamento generale sulla protezione dei dati; *iii)* istituzione di una serie di controlli di qualità a diversi livelli per minimizzare gli errori e garantire l'integrità dei

dati al momento dell'inserimento degli stessi; *iv)* pilotaggio dello strumento da parte di 12 operatori sanitari esterni allo studio, a cui è stato chiesto di valutare e fornire riscontro sugli aspetti chiave dello strumento; *v)* verifica dell'efficienza della procedura di inserimento dati e dei controlli di qualità utilizzando i dati clinici disponibili da pratica clinica sugli utilizzatori di profilassi pre-esposizione (HIV-PrEP) che hanno avuto accesso al Centro MISTRA (AOVR), nel periodo compreso tra gennaio 2018 e settembre 2022. In merito all'inserimento dei dati, sono stati condotti procedimenti di inserimento manuale e automatico (attraverso l'importazione di un foglio Excel preesistente) al fine di verificarne separatamente la fattibilità. L'usabilità dello strumento è stata valutata tramite uno studio di implementazione che ha testato il sistema di immissione dei dati (riconciliazione dei dati) e l'elaborazione degli stessi attraverso analisi statistiche esplorative, incentrate sulla valutazione dell'impatto di COVID-19 sugli utilizzatori di PrEP in periodo pre-, pandemico, e post -pandemico.

Risultati: Sono stati sviluppati quattro strumenti (Dati demografici, Anamnesi, Visite Standard, Prescrizioni Antimicrobiche) che ospitano 7 moduli distinti. L'approccio modulare consente di ottimizzare le funzionalità future dello strumento, facilitando l'aggiunta di moduli intercambiabili, dinamici, ed indipendenti, senza impattare sulla struttura generale del sistema. Lo strumento Visita Standard (che include i moduli "comportamento sessuale", "HIV-PrEP", "segni e sintomi", ed "esami di laboratorio") è il nucleo chiave del sistema. In virtù della modalità longitudinale, lo strumento "Visita Standard" viene compilato solo al momento dell'arruolamento, e può essere selezionato e compilato in momenti successivi (visite di follow-up del paziente), qualora necessario. Tuttavia, la caratteristica principale di questo sistema di raccolta dati è la possibilità di completare visite, con dati su diagnosi e trattamento, in base alle esigenze dei pazienti con poco onere per colui che raccoglie i dati. Il

processo di riconciliazione dei dati è stato lineare ed il 95% dei dati è stato importato con successo senza necessità di ulteriore revisione. Sono state condotte analisi esplorative includendo 256 utilizzatori di PrEP e 1595 visite. I risultati principali hanno mostrato una significativa diminuzione del numero di visite ed un aumento dell'interruzione della PrEP durante il periodo pandemico, rispetto ai periodi pre- e post-pandemici.

Conclusioni: Lo studio ha portato all'implementazione di uno strumento sicuro e di facile utilizzo in grado di ospitare dati standardizzati di alta qualità. Lo strumento mostra una vasta gamma di applicabilità sia in ambito di ricerca sia clinico, da adottare in caso di future emergenze sanitarie, informando rapidamente processi decisionali e supportando la pratica clinica grazie all'implementazione della telemedicina.

ABSTRACT

Background: The Coronavirus Disease 19 (COVID-19) pandemic has severely impacted sexual health service provision with consequences at both individual and public health level. The collection of real-time high-quality data is of utmost importance to monitor the impact on service delivery and disruption in case of future health emergencies.

Aims: This is a 3-year study, implemented in the framework of a broader collaboration between World Health Organization (WHO) Department of Sexual and Reproductive Health Research and University of Brighton (UOB) with the University Hospital Verona (UHVR). The overarching study aim was to develop and pilot a secure, standardised, web-based electronic case report form (eCRF), *via* Research Electronic Data Capture (REDCap) system, for sexually transmitted infection (STIs) and HIV clinical data management. The eCRF constituted the basis for a research infrastructure aimed at conducting multi-centric implementation studies able to answer selected research questions and guide decision making processes.

Methods: The eCRF construction required a multidisciplinary approach (9 study experts from UHVR and UOB with different backgrounds) and consisted of a series of distinct steps: *i)* identification of a minimum set of standardised HIV-STIs core variables required to increase study consistency; *ii)* design of the eCRF framework according to literature key-principles with particular focus on a structure based on modularity, longitudinal mode, flexibility, intuitive workflow, and compliance with the General Data Protection Regulation; *iii)* set up of a series of quality checks at different levels to minimise errors and ensure data integrity at time of data entry; *iv)* eCRF piloting by 12 healthcare providers external to the study, who were asked to assess and provide feedback on key eCRF aspects; *v)* testing of entry procedure and quality checks efficiency using clinical routine data on HIV-

Pre-Exposure Prophylaxis (PrEP) users accessing UHVR Centro MISTRA from January 2108 to September 2022. Mixed manual and automatic entry processes (with import of a pre-existing Excel sheet) were performed for checking feasibility of both tasks. The tool usability was evaluated *via* an implementation study which tested data entry system (data reconciliation) and data processing through exploratory statistical analyses, which focused on the assessment of COVID-19 impact on PrEP users in pre-pandemic, pandemic, and post-pandemic periods.

Results: Four instruments were developed (Demographics, Past Medical History, Standard Visits, Antimicrobial Prescription) hosting 7 modules. The modular approach was used to test the current set of instruments and, in the future, to add further functionalities allowing an interchangeable, dynamic, and independent modules development without impacting the overall eCRF frame. The repeatable Standard Visit instrument (including sexual behaviour, PrEP intake, signs & symptoms, and laboratory assessment modules) is the eCRF core. Given the longitudinal mode, baseline instrument is populated only at enrolment and then can be further filled in at various time points (patient follow-up visits), if needed. The core eCRF feature is the possibility of completing visits based on patients' needs with little burden for physician or data collector. The reconciliation process uploading already collected data into the eCRF was straightforward with 95% of successful import without need of further review. Exploratory analyses were conducted on 256 PrEP users and 1595 visits. Main findings showed significant decrease in visits number and increase in PrEP discontinuation during pandemic period.

Conclusion: The study led to the implementation of an easy-to-use eCRF able to host standardised, real-time, high-quality data. The eCRF suggests a wide range of applicability in both research and clinical areas to be adopted in case of future health emergencies, potentially useful to guide clinical decision-making and support healthcare practice with telehealth implementation.

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INTRODUCTION

Global response to COVID-19 pandemic

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in the city of Wuhan, in the Hubei Province (China). The virus quickly spread, leading to an epidemic throughout China, followed then by a global pandemic. The World Health Organization (WHO) first declared Coronavirus Diseases 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) as a global health emergency in January 2020.

At a news briefing in March 2020, WHO Director-General Dr. Tedros Adhanom Ghebreyesus, noted that over the past two weeks, the number of cases outside China increased 13-fold and the number of countries with cases raised threefold, and further increases were expected. He declared that the WHO "is deeply concerned both by the alarming levels of spread and severity and by the alarming levels of inaction," and he invited the countries to take action to contain the virus spread. "We should double down," he said. "We should be more aggressive." On March 11th WHO announced that the viral outbreak was officially a pandemic, the highest level of health emergency (1).

The clinical features of COVID-19 vary significantly between individuals from asymptomatic to severe and critical disease. Especially in the vulnerable populations, *e.g.* elderly, patients with concomitant illnesses or immunocompromising conditions, COVID-19 might clinically worsen to pneumonia and severe life-threatening complications characterised by acute respiratory distress syndrome, multisystem organ failure, and death (2).

The COVID-19 pandemic represents an unprecedented challenge to the scientific community, the health system, and the public health institutions. A proper and successful management of this emergency has required the

application of novel research frameworks and integrated knowledge involving different research fields, such as basic, clinical, public health, and implementation sciences (3,4).

WHO and other international organisations have worked closely with global experts, governments, and partners to expand and constantly update scientific knowledge on the SARS-CoV-2, to track its spread and virulence, and to provide advice to countries and individuals on public health measures to protect health and prevent the spread (5,6).

Pharmaceutical companies have worked to accelerate the Research & Development of vaccinations, diagnostics, and therapeutics for use against COVID-19. Numerous research initiatives were established in record time, working with academic groups, start-ups, and vaccine manufacturers to find and test preventative tools.

Moreover, several regulatory agencies have reviewed marketing authorisation applications and adopted agile and flexible ways of working to accelerate the approval of promising medical products for clinical use. The United States (US) Food and Drug Administration (FDA), for example, ensured rapid access to treatment for patients through the creation of the Coronavirus Treatment Acceleration Program, responsible for the rolling review process (7,8).

Since early 2020, a wide range of non-pharmaceutical interventions were deployed by local or national governments and international bodies to different degrees and lengths, according to the various pandemic waves and surges of contagion. They include, for example, social distancing, mandatory mask wearing in many public places, travel restrictions or even bans, closures of schools and other public services, establishment of curfews, complete lock-downs, and isolation of cases and contact tracing (9).

On the one hand, such interventions have proved to be effective in reducing the direct impact of COVID-19, by minimising the exposure of individuals to SARS-CoV-2 and therefore decreasing the number of COVID-19 cases potentially requiring hospitalisation or leading to death. At the same time, the application of these measures has allowed to buy time for development and approval of the therapeutics. On the other hand, the implementation of the containment strategies has had a drastic impact on health and well-being at individual level, but also more broadly on societies and economies across the world.

Impact of COVID-19 on health

By December 2022 there have been 651.918.402 confirmed cases of SARS-CoV-2 infection globally, and nearly 7 million people have died (10). These numbers probably underestimated the real overall health impact of the pandemic, given that several cases and deaths went and are going undetected mainly because of poor capability of testing, especially in resource-poor countries.

Since early 2020, the world has been hit by several peaks in SARS-CoV-2 infections and in associated deaths: most European countries and US experienced peaks in infections and deaths in late 2020 an early 2021, while Asia-pacific countries experienced peaks late in 2021. The difference in timing and magnitude of these waves across countries and regions is related mainly on the heterogeneous preparedness and response to the pandemic, the unbalanced vaccination coverage, and the fragmentation of the health system unable to adapt the ongoing challenges (11,12).

A crucial indicator of the true death toll related to COVID-19 is the excess mortality, calculated as the difference between the number of deaths that have occurred and the number that would be expected in the absence of pandemic based on data from earlier years. This measure incorporates both

deaths associated with COVID-19 directly (due to the disease) or indirectly (due to the pandemic's impact on health system and society). Deaths linked indirectly to COVID-19 are attributable to other health conditions for which people were unable to access prevention and treatment. Although reported COVID-19 deaths in the 24-month period (2020-2021) totalled 5,94 million worldwide, WHO estimated 14.9 million excess deaths for the same timeframe globally, indicating that the full impact of the pandemic is much greater (13). A recent systematic analysis study found similar results at global level and observed that the number of excess deaths were largest in lower income countries (South Asia, Middle East, North Africa) (14).

A wide range of long-term effects have been reported following a full recovery from acute SARS-CoV-2 infection, including a myriad of symptoms and syndromes, often referred to as "long COVID" (15). In response to the wide range of symptom constellations included in varying definitions for 'long COVID', WHO further applied the Delphi methodology to develop a consolidated clinical case definition, applying the specific terminology 'post COVID-19 condition': "*a condition occurring in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others which generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID-19 episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time*" (16).

The number of individuals living with post COVID-19 conditions globally is unknown. Data from the US Centre for Disease Control and Prevention (CDC) estimated 7.5% of adults were still experiencing persistent symptoms three or more months after the COVID-19 diagnosis. A recent systematic

review and meta-analysis including 195 studies showed that 45% of COVID-19 survivors, regardless of the hospitalisation status, were experiencing a range of unresolved symptoms at four months (17).

Post COVID-19 conditions pose a threat for the healthcare systems, which are already compromised following the acute phases of the COVID-19 pandemic. Moreover, their management is challenging to healthcare providers (HCPs) (18). Published literature has described over 50 post COVID-19 condition symptoms (19–21), many of which are debilitating and have a strong negative impact on mental health and quality of life. (22) The most prevalent symptoms include fatigue and breathing difficulties, followed by taste and smell disturbances, chest pain, headache, cognitive impairment, memory loss, and sleep disorders (15,19). Post COVID-19 condition symptoms can occur in clusters, while some patients might experience multiple outcomes, and multiple organ systems can be affected simultaneously.

Impact of COVID-19 on health systems

The COVID-19 pandemic, in addition to the direct disease burden, carries a significant risk of indirect morbidity and mortality from other preventable and treatable diseases as result of essential health services fragmentation. Countries reported disruptions across services for all main health areas including sexual, reproductive, maternal, new-born, child and adolescent health, immunisation, nutrition, cancer care, mental, neurological and substance use disorders, tuberculosis, malaria, neglected tropical diseases, and care for older people. Additionally, even as COVID-19 vaccination has scaled up, increased disruptions were reported in routine immunisation services.

The WHO *Global pulse survey on continuity of essential health services during the COVID-19 pandemic* conducted in 192 countries across Europe

Region revealed that, between February and August 2020, 92% of countries experienced some form of disruption. Disruption and backlogs affected a wide range of services, primarily the hospital services, dental care and mental health services, and lately mainly primary care and emergency care (23).

The disruption of health care systems was particularly relevant in the initial months after the pandemic's onset in March 2020. Health systems underwent major changes, such as postponement or cancellation of elective procedures and non-urgent medical care, the closure of medical practices, while public health messaging emphasised avoiding unnecessary healthcare use to reduce exposure to the virus and conserve limited resources. These measures, combined with shelter-in-place orders, resulted in sweeping reductions to hospitalisations, accident and emergency department (ED) attendances, and primary care appointments across a wide spectrum of medical conditions (24,25).

The consequences of COVID-19 on internal medicine and surgery care during pandemic were dramatic. For example, COVID-19 has caused several countries to suspend the colorectal screening: a study based on data from the United Kingdom (UK) national database showed an 88% decrease in endoscopy procedures (26). A global study on cancer patients found that a treatment delay of four weeks is associated with a 6-13% increase in the risk of death, whilst delays of up to twelve weeks further increase this risk. In breast cancer, for example, an eight-week delay in surgery increases the risk of death by 17%, while a twelve-week delay increases it by 26% (27). During the COVID-19 pandemic, there was a significant decrease in acute admissions for cardiovascular diseases across all European countries: more precisely, hospitalisations decreased by 31% for acute coronary syndromes, 34% for acute heart failure, and 32.3% for arrhythmias. Patients admitted to

the ED had a much higher mortality risk (4-time higher death risk) during the COVID-19 outbreak (28).

Sexual and Reproductive Health

Reproductive health is defined as *"A state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity, in all matters relating to the reproductive system and to its functions and processes*". Reproductive health implies that people are able to have a satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when and how often to do so (29).

WHO recently defined sexual health as *"a state of physical, emotional, mental, and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction, or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination, and violence. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled*." *WHO, 2006* (30). Sexual health is fundamental to the overall health and well-being of individuals, couples, and families, and to the social and economic development of communities and countries. Sexual health, when viewed affirmatively, requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination, and violence. Moreover, sexual health is not a fixed state of being, and every person's needs will change across the life course. For this reason, it is crucial to undertake a range of activities across this continuum: from support of sexual well-being to prevention and management of disease. A valuable sexual and reproductive health (SRH) involves gender equality, respect, safety and freedom from discrimination, violence, and stigma. It is

critically influenced by power dynamics, gender norms and expectations and is expressed through diverse sexualities.

SRH is important across the life course and represents a concern for both women and men, from infancy to old age. A proper and constant support of SRH throughout the life cycle is therefore essential and it can be achieved by the promotion of services across a variety of sectors. These sectors go from health, including the health workforce, to education systems and the development of specific programmes, including comprehensive sexuality education, family planning, pre-conception care, antenatal and safe delivery care, post-natal care, services to prevent sexually transmitted infections (STIs, including Human Immunodeficiency Virus, HIV), and services facilitating preventive screening, early diagnosis, and treatment of reproductive health illnesses. All efforts for supporting SRH service delivery rely on skilled HCPs who should provide timely, high-quality, and respectful care that is also affordable and accessible, functional health infrastructure, integration with other services and the availability of essential health supplies such as contraceptives, life-saving medicines and basic medical equipment (31).

Numerous international non-profit organisations are working on improving SRH and ensuring equal access to SRH services across the world, such as the CHOICE for Youth and Sexuality (https://www.youthdoit.org/themes/sexual-and-reproductive-healthand-rights-are-human-rights/), WHO Sexual and Reproductive Health and Research (https://www.who.int/teams/sexual-and-reproductive-health-and-research-(srh)/areas-of-work) in collaboration with its partners: United Nations Sexual and Reproductive Health Agency (UNFPA, https://www.unfpa.org/sdg), United Nations Development Programme (UNDP, https://www.undp.org/), United Nations Children's Fund

(UNICEF, https://www.unicef.org/), and the World Bank (https://www.worldbank.org/en/home).

Impact of COVID-19 on Sexual and Reproductive Health

COVID-19 pandemic has had dramatic effects on well-being of the world population across all SRH dimensions, due to the implementation of restriction measures and the disruption of delivery and use of SRH services, including comprehensive abortion and post-abortion care, pre and post-natal check, family planning/contraception, and HIV-STIs prevention and treatment (32).

Prior infectious disease outbreaks have impacted the demand for, provision of, and access to SRH services. Lessons from the Ebola and Zika virus outbreaks, for example, have outlined the severe fragmentations in SRH services that exposed women and adolescents to preventable health risks (33). Since the beginning of the COVID-19 pandemic, some services were unavailable due to either facilities and health workers being repurposed to care for patients with COVID-19, patient safety concerns, movement restrictions disrupting travel to health facilities, supply chain fragmentations or a reduction in health workers because of increasing numbers being themselves infected by COVID-19 (34). Overwhelmed with COVID-19 cases, clinical staff may not have the time or personal protective equipment needed to provide family planning counselling and commodities (35). In addition, clients are refraining from visiting health facilities due to movement restrictions or fears about COVID-19 exposure.

Abortion, sexual and gender-based violence, and contraception

The precise impact of COVID-19 at global level is unclear. In low-income and middle-income countries, the UNFPA estimates suggested that disruptions lasting 3–6 months in 2020 left between 4 and 23 million women

unable to access modern contraceptives, a projected 1.4 million (500000–2.7million) unintended pregnancies, and an additional 31 million cases of sexual and gender-based violence (SGBV) (36,37).

A variety of state-level restrictions were placed on abortion care in response to the COVID-19 pandemic, leading to reduction in utilisation and delays in time to abortion. Other pandemic-related factors may have also affected receipt of abortion care, potentially exacerbating existing barriers to care (38). Stay-at-home orders may have complicated travel to a clinic, especially among individuals requiring childcare. Moreover, several states explicitly targeted surgical abortion (as opposed to pharmaceutical abortion) as part of their COVID-19 restrictions. These states included these procedures as prohibited elective surgeries that could be reasonably deferred until after the pandemic had subsided (39). The risk for SARS-CoV-2 exposure may have discouraged some individuals from seeking any medical care, including for abortions, especially among those whose household members have pre-existing health conditions that increase their risk for severe COVID-19. Several large-scale studies conducted mainly in lower income countries reported decreases in safe abortion services during COVID-19. A UNICEF study using representative data for South Asia reported declines of 6% and 43% in safe abortion services in Q1 and Q2 of 2020, respectively (40), and similar results were found in Mexico and India (41,42). Data from Marie Stopes International (MSI) Reproductive Choices, one of the major private abortion providers, showed that 1.9 million women and girls have lost access to its contraception and safe abortion services in the first half of 2020 due to the COVID-19 pandemic. Across the 37 countries where it works, MSI estimates that the loss of its services in 2020 might have led to 3 million additional unintended pregnancies, 2.7 million additional unsafe abortions, and 11.000 additional pregnancy-related deaths (43).

The COVID-19 pandemic has exposed the vulnerability of global contraception provision, exacerbating the barriers to access reproductive health services, leading to suspension of clinical services and disruption of supply chains (37). The traditional pattern of face-to-face contraception consultation, in fact, underwent a forced change in several countries across the world. Initial 2020 UNFPA estimates of the magnitude of the impact of these factors in lower income countries suggested that between 13 to 51 million women would be unable to use modern contraceptives depending on the duration of lockdowns (3, 6, 9 or 12 months) and the severity of the disruption (low, medium, or high) (36). All available studies in literature reported some declines in contraception provision of varying magnitude depending on setting and income. A retrospective analysis of English data between 2019 and 2020 showed that prescription of the combined oral contraceptive pill reduced by 22% during the period of lockdown compared to the same three months in 2019 (44). An online survey observed that over one in three women aged 18–30 years in Ghana, Kenya, Uganda, and Zimbabwe needing family planning reported that COVID-19 affected their access to these services (34% in Ghana, 41% in Kenya, 46% in Uganda, and 38% in Zimbabwe) (45). A further study described issues in accessing contraception during the pandemic for young contraceptive users in Kenya (35% of adolescent girls and young women and 40% of adolescent boys and young men), and counselling on the side effects of contraceptive methods was also negatively affected (46).

SGBV has intensified since the outbreak of COVID-19 across the world. On March 27, 2020, the United Nations (UN) issued a warning statement that domestic violence may have risen due to the restrictive measures implemented to control COVID-19 and called on governments to increase efforts to address the rising risks of violence (47). Lockdowns and the other mobility restrictions, in fact, have left many women trapped with their

abusers, isolated from social contact and support networks. Increased economic precarity has further limited many women's ability to leave abusive situations. According to the Rapid Gender Assessment Surveys conducted by UN women (https://www.unwomen.org/en) in 2020 across 13 countries with different incomes (Albania, Bangladesh, Cameroon, Colombia, Côte d'Ivoire, Jordan, Kenya, Kyrgyzstan, Morocco, Nigeria, Paraguay, Thailand and Ukraine), 45% of participating women have been exposed directly or indirectly to at least one form of violence since the pandemic onset, and the most vulnerable groups were the younger women aged 18-49 years and women living with children (48). 2020 data from UNFPA indicated that there has been a 30% increase in reported cases of GBV globally from the beginning of the pandemic, and according to the latest projections, that 31 million additional cases of GBV could be expected to occur if the lockdown had continued for at least 6 months (49). Certain groups of women are more likely to be victims or experience GBV, namely domestic workers, older women, women with disabilities, women without access to technology, and women facing housing precarity and violence because of an intersection of marginalisation and discrimination, as stated by the Human Rights Watch (50).

HIV-STIs testing and treatment services for key-populations

The COVID-19 pandemic has had a complex and profound effect on individuals and their access to sexual health services. During the pandemic, several countries enforced strict stay-at-home policies, which has had the effect of keeping selected individuals (*i.e.* HCPs and emergency workers) from getting the resources that they needed (51). Whilst lockdowns were imposed, studies constantly revealed that sexual activity was still ongoing during the pandemic, especially among the five key-populations (men who have sex with men (MSM), sex workers, people in prisons and other closed settings, people who inject drugs, and trans and gender diverse people).

Stephenson *et al.* reports from a questionnaire evaluating sexual behaviours during the pandemic amongst MSM, some respondents reported an average increase of 2.3 sexual partners, with some participants having unprotected sexual intercourse (52). A survey investigating the sexual behaviour among MSM during the first national lockdown (March – July 2020) in UK revealed that 17% of participants reported multiple condomless anal intercourse (53). A study with 1301 Portuguese MSM found that approximately 20% had engaged in chemsex with casual partners during the lockdown (54).

Several studies showed a decreased access to sexual health services because of physical restrictions and re-prioritisation within national health-care settings. An online survey of Nagendra *et.al* found out that as of April 2020 only one fourth of HIV-STIs testing points were accessible to clients (55). The study of Santos *et al.* including 2732 gay men and other MSM from 103 countries described comparable findings. Upon investigating the access to HIV-related services among MSM, the study showed that 23% of the participants lost the link to HIV care as a result of the social isolation policies (56). The same study observed that MSM experienced greater difficulty in accessing condoms during the lockdowns (56). Further exploration into the fragmentation of sexual health services from Pinto *et al.* found that routine testing of gonorrhoea and chlamydia had been suspended in the pandemic period, with decreases of 59% for female patients and 63% for male patients, at the beginning of April 2020 (57). The report of UK Department of Health and Social Care found that, between January and June 2020, comparing data from sexual health services and chlamydia testing laboratories with complete data reported for both January to June in 2019 and January to June in 2020, there was a 30% reduction in tests for chlamydia, gonorrhoea and syphilis at sexual health services compared to the same period in 2019 (58). Two retrospective observational quantitative studies conducted in Belgium and China reported a decrease in the number of HIV tests conducted with

pandemic progression, indicating an interruption in the regular HIV care *continuum* (59,60).

The provision of antiretroviral therapy (ART) service for people living with HIV (PLHIV) was also compromised during the first pandemic waves, despite with lesser extent. In Zimbabwe, a highly-HIV burdened country, about 19% of PLHIV who attempted to get their ART refills were not successful during the lockdowns (61). Conversely, a recent CDC analysis demonstrated that the provision of highly effective ART remained strong, and the proportion of people linked to care after they received an HIV diagnosis remained stable in the timeframe 2019-2021 in US (62). Summarising, the available evidence showed that barriers to accessing care were extended and were associated with unmet sexual health service needs, especially for individual reporting sexual risk behaviours, which mostly should benefit from regular care.

Impact of COVID-19 on epidemiology of STIs

A common-sense perspective suggests the possibility for contracting STIs during the pandemic should be much reduced considering COVID-19 restrictive measures and interventions. However, as sexual desire is an essential human need, it is implausible to assume sexual contact ceases for the duration of the pandemic. The reduced availability of services during the COVID-19 pandemic for preventive, HIV-STIs testing, and treatment services reported by several countries has caused a resurgence of STIs and in some contexts the emergence of non-classical STIs globally. Despite with some differences, countries with well-established STIs surveillance systems such as the US, Canada, and UK have reported an increase in at least three STIs: syphilis, gonorrhoea, and chlamydia. UK Public Health Agency data revealed that bacterial STI test positivity increased during March and April 2020; 17% of tests in April 2020 were positive compared to 13% in April

2019. The increase in bacterial STI positivity in March and April 2020 may reflect the prioritisation of testing symptomatic patients (58). CDC data showed that during the stay-at-home orders, between March and April 2020, reported STIs cases dramatically declined, compared to the same 2-month period in 2019, probably because reduced screening activity or underreporting of infections. A resurgence in gonorrhoea and syphilis cases described later in the year 2020 suggested that overall STIs may have increased during 2020. The raising case counts registered in late-2020 may mirror an increase in service utilisation as sexual health services became again available, or alternatively a higher disease transmission during 2020 due to delay in accessing the service for diagnosis. Furthermore, in accordance with the initial restriction policy, sexual behaviours may have changed, including frequency of new sexual partners, leading to spread of sexual networks (63). Some models have been developed to assess the HIV-STIs rates in the post-pandemic period, showing different results. However, all showed service disruption as associated with increases in new HIV-STIs and emphasize the importance of continued care (64).

The epidemiology of STIs during the pandemic relies on several factors and the real incidence of STIs is hard to be defined. The decrease in testing during the COVID-19, the barrier to access sexual health clinics, the lockdown measures together with the clients' worries about attending the clinic during the pandemic have had an impact on HIV-STIs transmission dynamics. It is likely that such effects will persist for several more years and the full impact of the pandemic on STIs will be probably never completely identified.

Impact of COVID-19 on HIV- PrEP users

The evidence on the efficacy of HIV-PrEP in preventing the acquisition of HIV among the key-populations is supported by several randomised

controlled trials (RCTs) (65–67) and HIV-PrEP was therefore approved at different phases in several countries. In September 2015 the WHO recommended that individuals at substantial risk of HIV infection should be offered HIV-PrEP as an additional prevention choice, as part of comprehensive prevention approach, including HIV testing, counselling, male and female condoms, lubricants, ART for partners with HIV infection (68).

Having recognised the importance of HIV-PrEP as preventive strategy, the WHO and national public health agencies have put relevant efforts in establishing implementation strategies targeting both clients and HCPs, aimed at facilitating HIV-PrEP access and delivery, especially in at-risk individuals and in countries with higher HIV burden. Within the Global HIV Programme, the WHO has developed the HIV-PrEP implementation tool, containing modules for a range of stakeholders to support them in the consideration, planning, introduction, and implementation of oral HIV-PrEP (69). Similarly, the European Centre for Disease Prevention and Control (ECDC) made available operational guidance to support European Union/European Economic Area (EU/EEA) and the UK countries in the integration of HIV-PrEP into existing HIV prevention packages (70).

The global COVID-19 pandemic and associated lockdown measures might have created additional barriers to the continuity of HIV-PrEP delivery among key-populations. A study conducted at one of the largest HIV- PrEP-providing community health centres in US found that from January to April 2020, the over 3500 PrEP-using patients had decreased by 18%, HIV-PrEP initiation decreased by 72%, HIV-STIs testing decreased by 85%, and lapses in HIV-PrEP prescription refills increased by 191% (71). CDC analysis revealed that HIV testing and prescriptions for HIV-PrEP in US dropped substantially during the onset of the COVID-19 pandemic in 2020. HIV tests declined about 32% between the first and second quarters of the year, and

HIV-PrEP prescriptions fell about 6%. Testing and HIV-PrEP prescriptions started to rebound in the second half of 2020, but they did not reach pre-pandemic levels until early 2021 (62). The SARS-CoV-2-pandemic has impacted HIV-PrEP-users also with respect to their sexual behaviour compared to pre-pandemic period. Evidence available on the change of sexual behaviour is conflicting: although some studies suggested a reduction in sexual activity, other studies reported an increase of sexual encounters. An Australian study found that, among 847 HIV-PrEP users before the COVID-19 lockdown, 42% reported discontinuing HIV-PrEP after restrictions were put into place and the discontinuation of HIV-PrEP was associated with diminished sexual contacts (72). Conversely, a study among HIV-negative MSM reported that HIV-PrEP users are more frequently engaged in chemsex during the lockdown and had a higher number of sexual partners, compared to non-PrEP users (73).

The available evidence has described a common tendency in the reduction of HIV-PrEP use and access after the implementation of COVID-19 restrictions and this had implications on health and well-being of HIV-PrEP users. Moreover, from a public health perspective, this might have contributed to wider threats across the HIV prevention cascade. So far, most of the literature has focused on describing the immediate effects of pandemic in cross-sectional way, while little evidence exists on the potential long-term effects of pandemic on HIV-PrEP users after the relaxation of restrictive measures.

COVID-19 and telehealth

The WHO defines telehealth as "*the provision of health care services by health care professionals, utilizing technology to exchange information in the diagnosis, treatment and prevention of disease*." With the COVID-19 pandemic, the use of telehealth has become widespread in several aspects of

health-care delivery systems. Compared to face-to-face health-care services, telehealth may represent a valid alternative to provide care, reducing unnecessary exposure to COVID-19, help mitigate the spread of the virus, and reduce surges in hospitals and clinics. Telehealth can support physical distancing efforts and help ensure that care continues to be provided to those who need it most by triaging low-risk urgent care and follow up appointments, and maintaining continuity of care, especially for chronic disease management, and behavioural health patients, who may require routine access. The telehealth approach in the SRH field has been widely adopted during the COVID-19 pandemic, showing promising results. With respect to abortion, telehealth not only facilitates access for women seeking abortion services, but also provides the additional benefits of confidentiality and avoidance of stigmatisation, with similar clinical outcomes to facility-based management. (74) Telehealth has also helped bridge gaps in contraceptive care (75) and HIV-STIs testing deepened by COVID-19. A systematic review of RCTs including 5400 patients showed that sexual telehealth interventions among adolescents were found to increase self-efficacy for condom use and being tested for STIs (76). Since the pandemic, several countries have demonstrated substantial interest in implementing and scaling up telehealth services. To facilitate the diffusion of telehealth in the regular professional activity, national health systems have introduced regulatory flexibilities and incentives to encourage adoption and implementation, with coordination from providers and technology companies (77). Moreover, in response to the global increase in demand, the WHO made recently available an implementation guide providing an overview of key steps and considerations for implementing telehealth and optimising its benefits and impact in the common practice, beyond the COVID-19 pandemic (78).

Electronic data systems for research and COVID-19

Electronic data tool is a technology that is being widely used in clinical research all over the world. The benefits of data digitalisation are multiple, including timely reporting and communication, reliable and concise record keeping, availability of data at multiple health system level, standardised data collection with high quality, and faster and improved analysis. WHO strongly and globally encourages the strengthening of the capacity to collect, compile, manage, analyse, and use health data mainly derived from both population-based and institution-based sources. For example, the WHO SCORE for Health Data represents the most comprehensive strategies and interventions for strengthening country health information systems to address the national and subnational health priorities and identify critical gaps and needs by using simple, standardised, and verifiable core indicators (79). The COVID-19 pandemic has further underlined the need of timely and high-quality data (80). For example, analysis of electronic health records that capture real-time patient records of routine clinical care have resulted in better COVID-19 surveillance and produced evidence to inform public-health decisions. The COVID-19 pandemic has fostered several international collaborative efforts for real-world evidence research. For example, the international Consortium for Clinical Characterization of COVID-19 by HER (4CE) provided early data on disease progression of COVID-19 in about 28.000 patients (81). The WHO developed the Global Anonymised Clinical Data Platform for COVID-19, able to host data entered on a voluntary basis by HCPs, with the aim of addressing several clinical aspects of COVID-19, including the assessment of risk factors for severe disease, the description of treatment interventions, and the assessment of long-term sequelae (82). With similar purposes, the ORCHESTRA project funded by HORIZON 2020 has established an international cohort involving 37 partners from 15 countries with the aim to generate rigorous evidence to

improve prevention and treatment of COVID-19 and to better prepared for future pandemics (https://orchestra-cohort.eu/). The International COVID-19 Data Alliance aimed to build an open and trustworthy international research partnership to support a rapid response to COVID-19, and a long-term alliance for making data accessible to health researchers and scientists worldwide, enabling sharing data across 42 countries addressing urgent questions about pre-natal health during the lockdown (83).

Collaboration with WHO Department of Sexual and Reproductive Health and Research

The collaboration between UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme for Research, Development and Research Training in Human Reproduction (HRS), Department of Sexual and Reproductive Health and Research (SRHR) and The Epidemiology Unit, Infectious Disease (ID) Department, University Hospital Verona (UHVR) has started several years ago. One of the most relevant results of the collaboration was the SIALON II project, co-funded by the European Union, purposing to carry out and promote combined and targeted prevention complemented by a meaningful surveillance among MSM (84). Within the project, the SIALON II study was conducted, a complex multicentre integrated bio-behavioural cross-sectional survey targeting about 5000 MSM across 13 European cities, with concomitant collection of behavioural and biological data. The study provided an important contribution to the monitoring and evaluation of the HIV epidemic across Europe, integrating global acquired immunodeficiency syndrome (AIDS) monitoring indications within a second-generation HIV surveillance systems approach with the final aim of informing development and implementation of strategic, evidence-based HIV prevention campaigns for MSM (85). As crowning achievement of this long-lasting and fruitful collaboration, in September 2022 the WHO has

designated the UHVR as WHO Collaborating Centre for sexual health and vulnerable populations. The Collaborating Centre activities deal mainly with SRH with particular focus on vulnerable populations and its connection with mental health.

This PhD work was developed on the occasion of a further collaboration, which started in February 2020, when the UHVR joined the WHO SRH Human Reproduction Program (HRP) international project "*Health systems analysis and evaluations of the barriers to availability, utilization and readiness of sexual and reproductive health services in COVID-19 affected areas*". This 24-month project aims to longitudinally assess the impacts of COVID-19 on the health system's capacity to provide SRH services, targeting contraception, comprehensive abortion care, HIV-STIs prevention and treatment, and GBV care and support services available in local health facilities during the COVID-19 pandemic (34). The study pursues four main objectives: *i)* to explore the status of availability and the health facility readiness to provide services in contraception and abortion care, including the treatment of abortion-related complications and the provision of post abortion contraceptive care, HIV-STIs prevention and treatment, and support of women experiencing GBV in country regions/localities most affected by COVID-19; *ii)* to assess the availability and quality of services and barriers to the utilization of these services from clients' and HCPs perspectives in the selected COVID-19 affected areas; *iii)* to assess the post-pandemic recovery of the facilities to provide SRH services in comparison to the pandemic period; *iv)* to enhance the reproductive service capacity in COVID-19 through advocacy, policy briefs, media dissemination, and academic papers towards the national and regional stakeholders including policy-makers, academia, healthcare providers and the community. The study was carried out on two levels, at the individual and the health facility. The individual level involved clients (and their partners) and HCPs and used

qualitative methods of data collection. The health facility level involved a quantitative assessment (by means of adapted questionnaires) of infrastructure availability and readiness to provide SRH services and a qualitative survey to elicit HCPs perspectives of the same. The health system assessment adopted a repeated cross sectional survey design to capture any potential changes in SRH services availability during the COVID-19 epidemic within 9 to 12-months interval (baseline and endline) (34). Participating SRH centres are located in nine countries from different geographic areas and incomes: Brazil (Universidade Estadual de Campinas, São Paulo), Burkina Faso (Institute for Research in Health Sciences, Ouagadougou), China (Beihang University), Ghana (University of Ghana), Italy (UHVR), UK (School of Sport and Health Sciences, University of Brighton, UOB), Kenya (Aga Khan University, Nairobi), Pakistan (Aga Khan University, Karachi), Thailand (Khon Kaen University). The Italian centres, all located in the Verona City, were the following: Anti-violence centre P.e.t.r.a. (Pratiche Esperienze Teorie Relazioni Antiviolenza), Abortion Service, Family Planning and Contraceptive Service, Centro MISTRA (Centro Multidisciplinare per le Infezioni Sessualmente TRAsmesse).

The results of the project are being elaborated by WHO SRH staff. Results data are currently under WHO embargo and therefore not allowed to be presented at this time.

RATIONALE AND AIMS OF THE STUDY

This is an ancillary study of the ongoing WHO SRH HRP project. This study is the result of a longstanding collaboration between the UHVR and the UOB. The rationale behind the development of the study lies in the following elements:

1) *Longitudinal multicentric HIV-STIs data.* It has been recognised the need of collecting and sharing standardised longitudinal HIV-STIs data from common routine clinical practice in order to facilitate both clinical and research activities. The COVID-19 pandemic has further underlined how real-time high-quality data are strongly needed to address decision making.
2) *Longitudinal assessment of COVID-19 impacts.* The available evidence evaluating the impact of COVID-19 on SRH services provided mostly qualitative data from cross-sectional studies. Little literature has focused on a longitudinal and quantitative assessment of short and long-term impacts on SRH, in accordance with the pandemic trend and the relative restrictions adopted.
3) *HIV-PrEP users as target population*. This study focused on examining the impact of COVID-19 specifically on HIV-PrEP users on the basis of the following considerations: *i)* PrEP represents a key-strategy for preventing HIV acquisition and WHO actively promotes its implementation at global level (68); *ii)* WHO also estimated that one every four persons who would benefit from HIV-PrEP have been diagnosed previously with at least one STI before starting HIV-PrEP (86); *iii)* clinical guidelines recommend HIV testing every three months in HIV-PrEP users. In the light of these considerations, HIV-PrEP users are a key-population which accesses SHR services very frequently, for both scheduled and unscheduled visits and because of this they might have severely suffered from the SRH services interruption due to the COVID-19 pandemic.

The overarching aim of this study was to develop and pilot a standardised electronic collection report form (eCRF) with the following purposes:

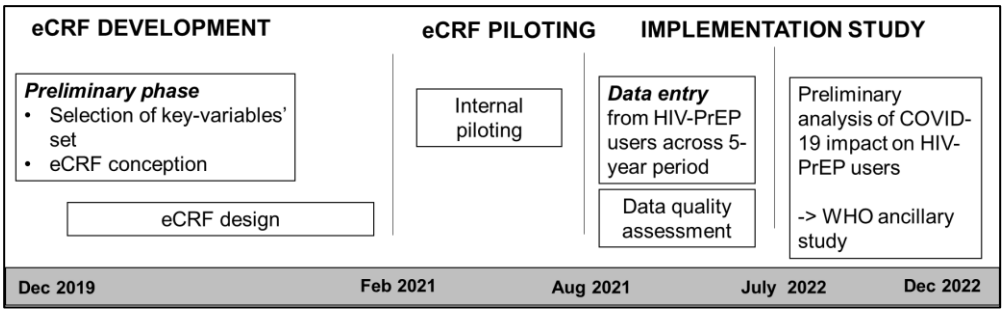
- ✓ To set up the basis for a research infrastructure hosting data of HIV-STIs individuals to create a multicentric international cohort for *i)* future implementation studies to efficiently address clinical key-questions or gaps; *ii)* for real-time informing both HCPs and stakeholders to guide clinical or public health interventions; *iii)* to improve clinical data management in the context of everyday clinical practice.
- ✓ To perform exploratory analysis on the COVID-19 impact on PrEP users in a highly burdened area.
- ✓ To identify a suitable telehealth approach to be applied in case of potential future health emergencies.

OVERVIEW OF THE STUDY

This is a 3-year study consisting of two different components, **Figure 1**. The first part focused on the stepwise development and piloting phases of a secure, standardised, web-based eCRF for clinical research data management, which has been implemented at the UHVR. The newly created eCRF was then populated with data from a longitudinal cohort of adult PrEP users accessing Centro MISTRA since January 2018 onward. The second part showed how to use collected data by providing an example of implementation study, which focused on the assessment of COVID-19 impact in HIV-PrEP users.

Centro MISTRA is a sexual health service, part of the UHVR Infectious Diseases Section. The centre targets both the general population, the vulnerable, and key-ones. The service offers a tailored counselling and testing for HIV and other STIs as well as the combined preventive approach for HIV-STIs, and the linkage-to-care for the treatment of chronic STIs.

Figure 1. Structure and timelines of the study



METHODS

Core study team

The multidisciplinary core team participating in the study was composed of nine members with different professional backgrounds: infectious disease, methodology, bio-statistic, health psychology, and public health. In general, the UHVR members were responsible for the entire study content and conduction, while UOB members were involved for consultations and advice regarding the key-steps of the project, **Table 1**.

Table 1. Study team members, roles, and tasks

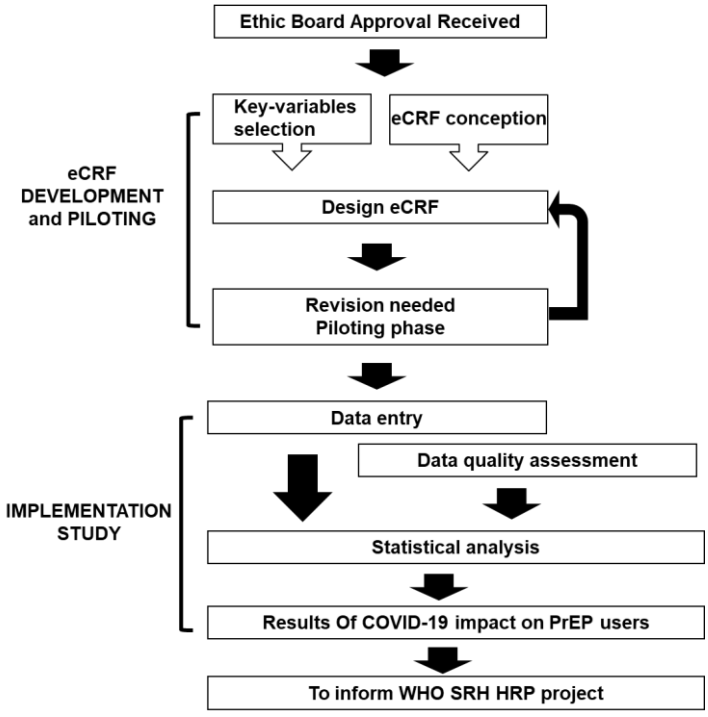
Study team member	Professional expertise	Affiliation and Role in the Study	Tasks
Alessia Savoldi, MD	ID clinician and researcher, HIV - STIs field	UHVR Study leader	Study conception and coordination, responsible for the entire study
Massimo Mirandola, Psychologist, PhD	Mental health, clinical epidemiology, methodology	UHVR Study co-leader	Study conception, eCRF development and validation, statistical analysis, methodology
Matteo Morra, MD	ID clinician and researcher, statistics	UHVR Study investigator	Data management, eCRF development and validation, statistical analysis
Maddalena Cordioli, MD, PhD	ID clinician and researcher, HIV-STIs field	UHVR Study investigator	Study conception, eCRF development and validation
Ilaria dalla Vecchia, MD	ID clinician	UHVR Data manager	Data management and coordination
Lucia Bonato, MD	ID clinician	UHVR Research assistant	Data entry
Laura Rovigo, MD	ID clinician	UHVR Research assistant	Data entry
Nigel Sherriff, Prof, PhD	Public health and health promotion	Principal investigator UOB site	Study conception, consultation
Alexandra Sawyer, Psychologist, PhD	Health psychology	Co-investigator UOB site	Study conception, consultation

The study received approval from the Ethics Committee of the UHVR (number 3349CESC) and from the WHO RP2 (number CERC 0103E) on 28th June 2021.

Development of the eCRF

The research infrastructure was built up by means of the Research Electronic Data Capture (REDCap®) system, which has been implemented at the UHVR since 2020. The REDCap platform is a novel workflow methodology, a secure, web-based software solution designed for rapid development and deployment of eCRF to support clinical and translational research (87). The whole process of eCRF development was based on the best-practice indications reported by the eCRF guidance, and in accordance with the regulatory requirements (including 2016 General Data Protection Regulation, GDPR). The workflow of the research infrastructure is displayed in **Figure 2**.

Figure 2. Research infrastructure workflow within the REDCap platform



Preliminary phase

A series of virtual meetings with *ad hoc* consultations with the core study team members were held on a bi-weekly basis to discuss the preliminary steps of the eCRF development, including *i)* the identification of a key-variables' set to be entered into the eCRF, and *ii)* the conception of the eCRF architecture.

Minimum set of study variables

The process of the identification of key-variables' set consisted of several steps. The entire process aimed to identify a minimum set of core variables that characterise prospective studies on HIV-STIs independent of the hypotheses evaluated. The uniform and homogeneous reporting of these variables in prospective clinical research is expected to increase data quality and study consistency. A primary list of items was generated based on a combination of literature reviews, expertise, and clinical experience in the HIV-STIs field of the study team members (*step 1*). The items were presented according to specific domains: patient general characteristics and sexual history, sexual behaviour, HIV-STIs clinical presentation, HIV-STIs laboratory testing, PrEP use, compliance, and adverse events. In a second round, a restricted pool of items from each domain following the non-overlapping, simplicity, clarity, and measurability principles was selected by the study team (*step 2*). A cut-off level of 75% agreement was chosen to define the consensus. Possible disagreements were sorted out internally through an additional decisional round (*step 3*). After a detailed analysis of all variables with a multidisciplinary view, the study team identified a final set of ***essential variables*** - those that the study team advised should be reported in all HIV-STIs studies for addressing any research question- and ***recommended variables*** - those that were defined important but not mandatory for reporting (*step 4*).

Modularity approach

The study team agreed to structure the eCRF by distinct modules. In line with the main purpose of the research infrastructure, the modularity approach allows to easily integrate and combine smaller modules, that are independent of each other, into the main eCRF structure in a dynamic way. The modular approach also allows to incorporate additional future potential modules easily, without negatively impacting the eCRF frame. The eCRF contains the following modules:

- *Socio-demographics module*. This module is based on socio-demographic data collected routinely by Centro MISTRA. Personal data are kept under the firewalls of the Hospital Information Technology (IT) System and not directly linked to the database of the project (pseudonymised data).
- *Past medical history module.* This module collects information on concomitant chronic diseases and medications, allergies, and vaccination schedule.
- *Sexual behaviour module*. This module investigated the sexual pattern and behaviour, including information on sexual partners, on sexual intercourse, sexual habits (group sex, chemsex drugs).
- *PrEP intake module.* This module investigates the pattern of PrEP use, the compliance, and the adverse events or toxicity.
- *STI signs & symptoms module.* This module collects clinical data on clinical diagnosis of any suspected or microbiologically proven STI.
- *Antimicrobial prescription module.* This module includes the type and the dosage of antimicrobial therapy prescribed to a patient for a specific suspected or microbiologically proven STI.
- *Laboratory assessment module*. This module includes microbiological results of patients' specimens collected during the visit as well as biochemical parameters (*e.g.,* creatinine, proteinuria, glycosuria, liver enzymes) usually requested to check PrEP toxicity. It is based on the data generated routinely via hospital and it is in line with the good clinical

practice (GCP) guidelines approved by hospital internal quality assurance units.

eCRF design principles

The design of the eCRF followed the key-principles for a successful eCRF reported in the literature (88–90).

1) *Multidisciplinary approach to achieve holistic vision*. The tool was designed with input from the study leader and other members of the core study team, including the person responsible for the statistical aspects of the study and team members who collected the study data.
2) *Longitudinal mode.* The repeating instruments and events module is a REDCap feature useful for collecting data multiple times using same instruments without set time points. This function is useful when data should be collected using the same instrument multiple times.
3) *Flexibility and dynamism to optimise data collection directly from common practice.* The tool is flexible and dynamic, enabling a smart collection of data directly from the electronic clinical chart or real-life during the visit. The interface reflects the flow of a usual PrEP visit, minimising in this way the burden of data entry and the errors.
4) *Intuitive interface and efficient workflow to ease data entry*. The interface is intuitive, user-friendly, and graphically appealing as well as data flow is effective and immediate for user navigation so that minimum training for study staff would be required and at the same time the data entry errors would be minimised.
5) *Collection of more quantifiable and less irrelevant data.* The tool is based principally on closed-ended questions, it means that the data entry clerk chooses among pre-defined standardised set of choices, in order to avoid any uncertainty. The open-ended questions with free-form text were adopted only exceptionally, in order to minimise the heterogeneity of collected data. In this way, the data collected are comprehensive, complete, and reliable.

6) *Automated error detection (edit checks) to improve overall data quality.* Both univariate and multivariate edit checks are applied (see paragraph: Quality Checks, page 43).
7) *Compliance*. The tool is compliant with the GCP, a set of internationally recognised, ethical and scientific quality regulatory requirements (see paragraph: Regulatory requirements and GDPR, page 44).

eCRF piloting

Before starting to enter data, a piloting phase occurred, with the aim of assessing the overall functionality and usability of the tool. The eCRF was piloted by 12 HCPs external to the study team and therefore not familiar with the tool. As part of the piloting, the core study team was offered training on the cohort purpose, design, quality assurance, reporting mechanisms, and data collection tools. The training included, for example, the importance of epidemiology (in cohort study design) to improve the quality of data entry, the importance of reviewing data indicators, as well as data verification, error checking, and storage. The testers were asked to comprehensively assess the eCRF structure and content while entering data of same subjects taken from hospital clinical charts. The following aspects were evaluated: *1)* general workflow and design; *2)* consistency and fluency in the data entry process; *3)* detection of some mistakes, unclarities or inconsistencies. Moreover, testers were asked to actively provide suggestions to improve the eCRF. All comments and suggestions provided by testers were elaborated and discussed by the study team and corrections made accordingly.

Data management

Data source

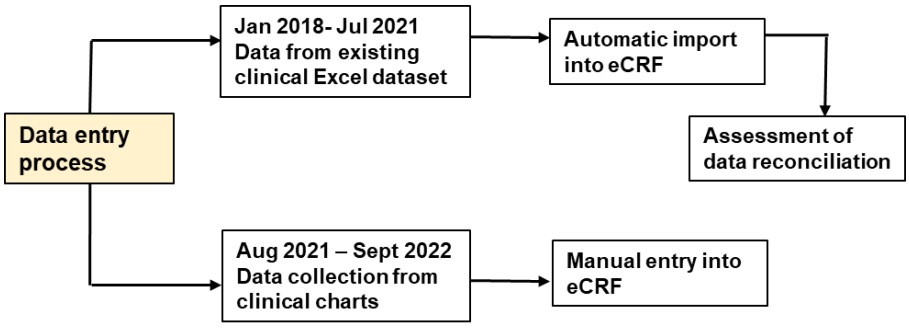
Data were obtained from the ongoing, longitudinal, monocentric HIV-PrEP cohort, which includes patients assuming oral PrEP with tenofovir disoproxil fumarate and emtricitabine aged ≥ 18 years which accessed the

Centro MISTRA since January 2018 onward and signed the written informed consent (IC) of the patient data register REGIST (Register of Sexually Transmitted Infection). Within the REGIST, patients agreed that personal and clinical data routinely collected for clinical practice can be used for research purposes, after appropriate de-identification. This study was approved by the UHVR ethical board.

Data entry

The data entry process was a composite process. Clinical and laboratory data of patients included in the PrEP cohort from 1st January 2018 to July 2021 were regularly entered at each PrEP evaluation into a pre-defined excel sheet as part of common practice of Centro MISTRA clinical staff. The second part of the data entry process was actively performed by four members of study team, collecting data of the time-frame August 2021 to July 2022. Personal, clinical, and laboratory data of each PrEP user were gathered from clinical chart, de-identified, and entered into the eCRF at baseline and at all the available follow-up visits, **Figure 3**. Overall, data from 1st January 2018 to 31st September 2022 were entered. This differentiation of the data entry process was intentionally performed with the purpose of testing the eCRF feasibility of both manual data entry and automatic import of a dataset into REDCap platform to check the reconciliation data process.

Figure 3. Frame of data entry



Quality checks

Data quality was ensured at different levels.

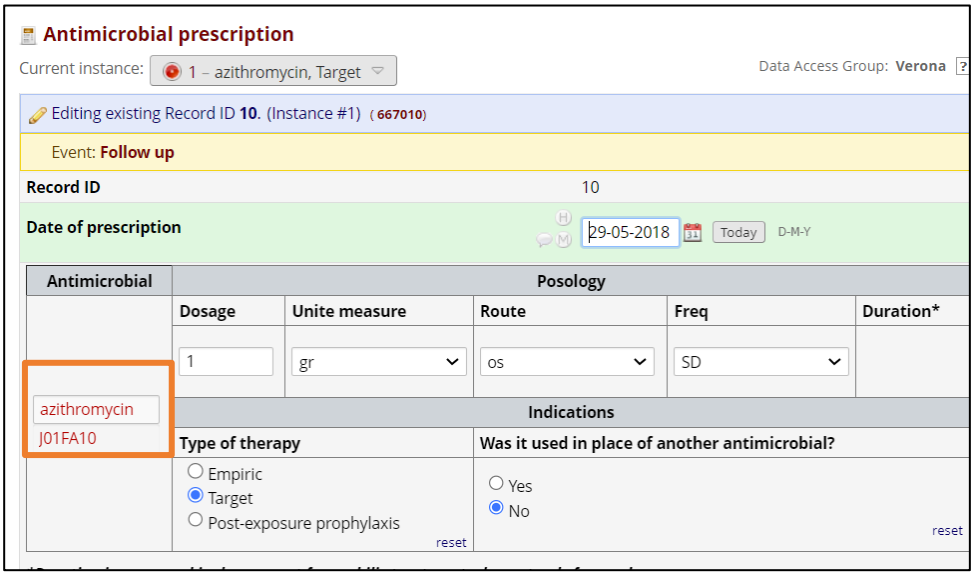
The eCRF was designed so that data integrity checks occur at the point of data entry (warning and alert). This was achieved by determining data quality rules and allowable field values for a single variable or a group of variables. The univariate edit check targets a single field or a single variable. For example, a minimum and maximum of valid range of values (validation rule) were set for some fields deemed to capture laboratory test results. Another example, validation rules were adopted to constrain the dates to a standardised format (dd-mm-yyyy). These rules immediately detected errors at data entry upon deviation from the accepted format. The multivariate check cross checks the entries across multiple fields/variables to ensure the data is logical and consistent.

When possible, as adjunctive validation rule, the entry data options into a specific field was linked to an external document, easily uploaded by REDCap, which includes a restricted pool of standardised items. For example, during the data entry, the antimicrobial type prescribed to patient can be chosen from options provided by the 2022 WHO Anatomical Therapeutic Chemical (ATC) Classification List (available at: https://www.whocc.no/atc_ddd_index/), **Figure 4** (page 44)**.**

Quality check in post-processing (query generation) phase were also adopted. As additional layer of data quality check, reports were used to point out missing data (usually a subset of them) or discrepancies of data of each included patient.

Reports were regularly run and shared with data manager and corrections integrated at different rounds during the data entry period.

Figure 4. Antimicrobial molecule entry in the selected field in accordance with the standardised options provided by 2022 WHO ATC list.



Moreover, an *ad hoc* eCRF guidelines document was developed and shared with study team. The document was intended to support the whole data entry process and ensure a consistent, standardised, accurate collection and recording of data. The document provided both general instructions and field-specific instructions for eCRF completion, addressing definitions, specifications for time points for observations, measurement methods, how to handle with mandatory/optional fields, and missing values. The eCRF guidelines document was built partly following the indications reported in the ICH E6 (R2) GCP scientific guideline (91).

Regulatory requirements and GDPR

GDPR is a regulation regarding data protection and privacy in the EU/EAA and the UK active since 2018, which aims to standardise and strengthen the protection of personal data. REDCap tool can be used to collect data subject in line with the GDPR, given that the tool is able to carry out the pseudo-anonymisation process, namely that the personal data are processed in a way

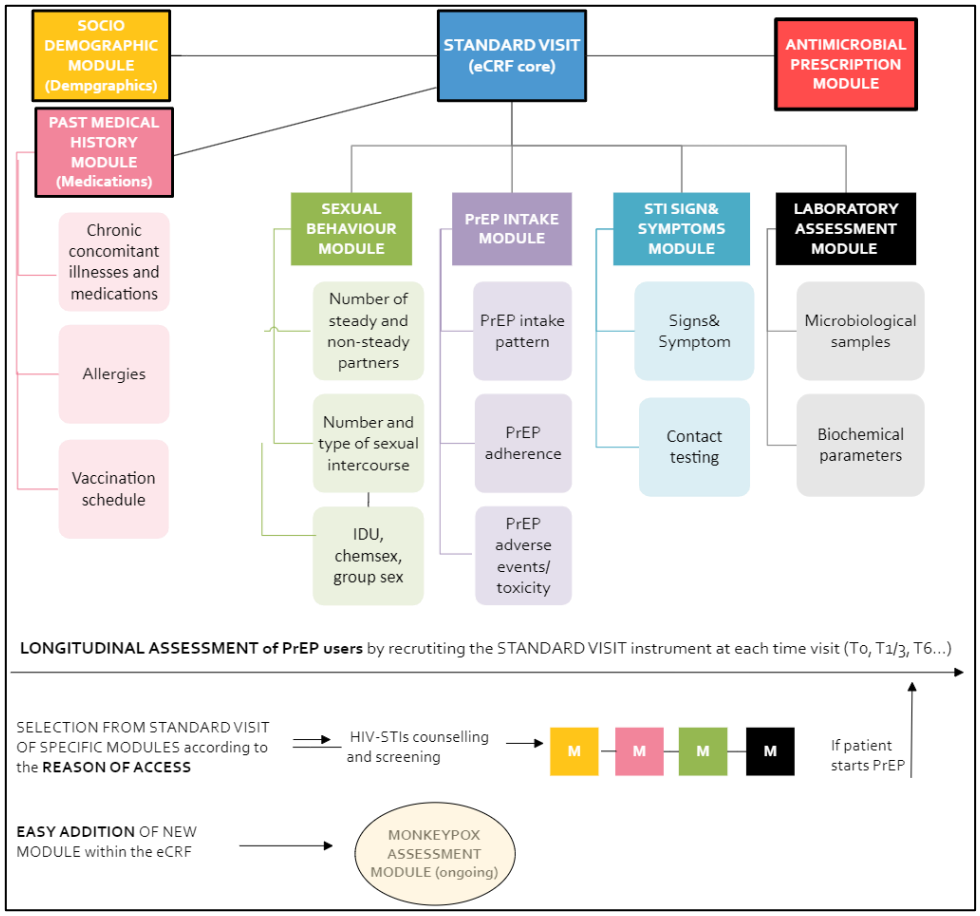
that this data cannot be attributed to a specific individual, by using a non-identifying participant ID or key-code. Unlike anonymisation, the pseudonymisation of personal data is intended to allow the reidentification of personal data when required or needed by the study investigator. All patient data captured were pseudo-anonymised and stored in the data management system at the UHVR according to local IT policy and data security. Only the research team had access to data, and they were not made available outside the team or institution. The data archiving system was in line with national, EU/EAA and international data legislations relating to the collection, storage, usage, and preservation of data, as well as data protection, data security and good management of data generated by researchers. Data were managed, stored, and destroyed in line with local requirements and ethics approvals. As part of this process, the study leaders ensured that the research team was aware of the data security regulations.

RESULTS

eCRF key outputs

Four specific instruments were developed within the eCRF hosting the seven modules described above. The instruments are the following: ***Demographics:*** including the socio-demographic module (not repeatable); ***Medications:*** including the past medical history module (not repeatable); ***Standard Visit***: including the sexual behaviour, PrEP intake, STIs signs & symptoms, laboratory assessment modules (repeatable), and ***Antimicrobial Prescription***: including the homonyms module (repeatable). The eCRF structure is displayed in **Figure 5** and **Figure 6** (page 48).

Figure 5. General structure and workflow of the eCRF



Advantages related to a modularity approach

The modularity plays a pivotal role in the optimisation of the eCRF functionality from both research and clinical perspectives. Some of the potential applications of the modularity approach within the eCRF are described below and summarised in **Figure 5** (page 46).

- *Longitudinal assessment by easily recruiting the Standard Module instrument at each visit.* For example, in case of PrEP user evaluations, the Standard Visit Instrument is completed at the baseline visit (T0) and easily be recruited at each follow-up visit (T1, T3, T6, T12, *etc*.)
- *Interchangeable and dynamic module use*. Some modules are designed to be in common with other HIV-STIs services provided by Centro MISTRA. The modules can, in fact, be singularly and independently selected in accordance with the clinical reason of access. For example, socio-demographic, past medical history, sexual behaviour, laboratory assessment modules can be used for data entry of a patient accessing the clinic for a HIV-STIs counselling and screening visit. In case of patient started PrEP at some point, module 3 will be then easily recruited for completion and linked with the other modules without strongly impacting on the general structure of the eCRF.
- *Easy module implementation.* New modules can be easily added without changing the eCRF frame and enabling a quick link with the already collected data (*e.g.,* Monkeypox assessment module is going to be incorporated into the eCRF).

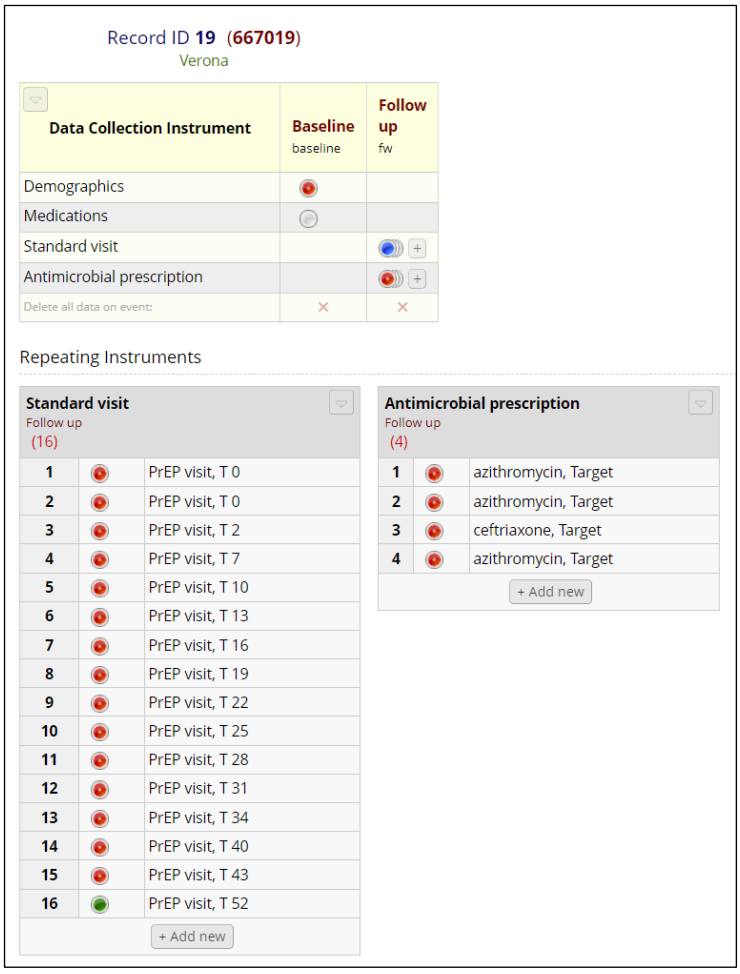
Standard visit

The Standard Visit instrument is the core of the eCRF. In the assessment of PrEP users, this instrument is recruited for baseline assessment and theoretically be repeated indefinitely, as long as the patient follow-up is active at the clinic. The longitudinal mode allows to create the form once

and then assign it to various time-points, that are not pre-defined, and to collect data longitudinally with little or no burden. The whole content of the Standard Visit is shown in the Annex, **Figure A1** (page 81).

The user-friendly and intuitive interface enables to outline at first glance the current state of the data collection process of a selected patient. This aspect can be also very useful from clinical perspective; the clinician, by opening the record, can immediately outline the current clinical situation of the patient. In the example reported in **Figure 6**, the Standard Visit instrument has been repeated for this specific PrEP user 16-time (2 baseline visits and 14 follow-up visits) for a total of approximately 4-year follow-up.

Figure 6. REDCap interface showing the eCRF instruments

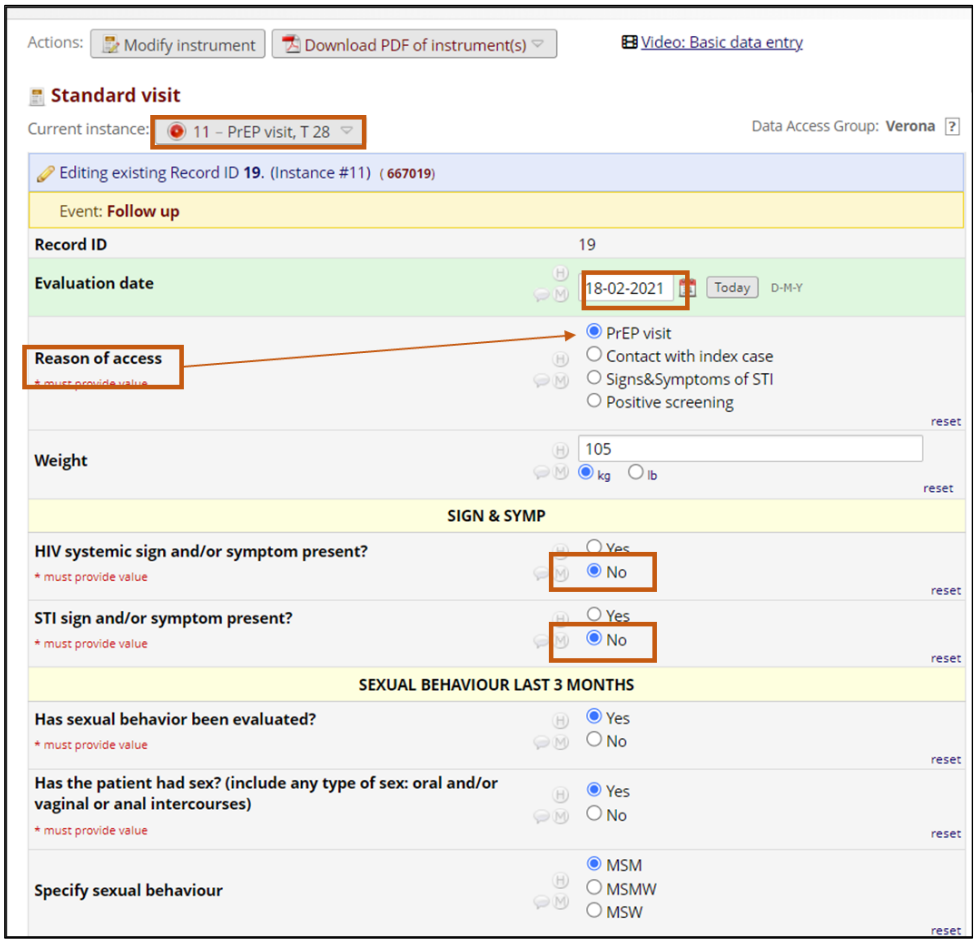


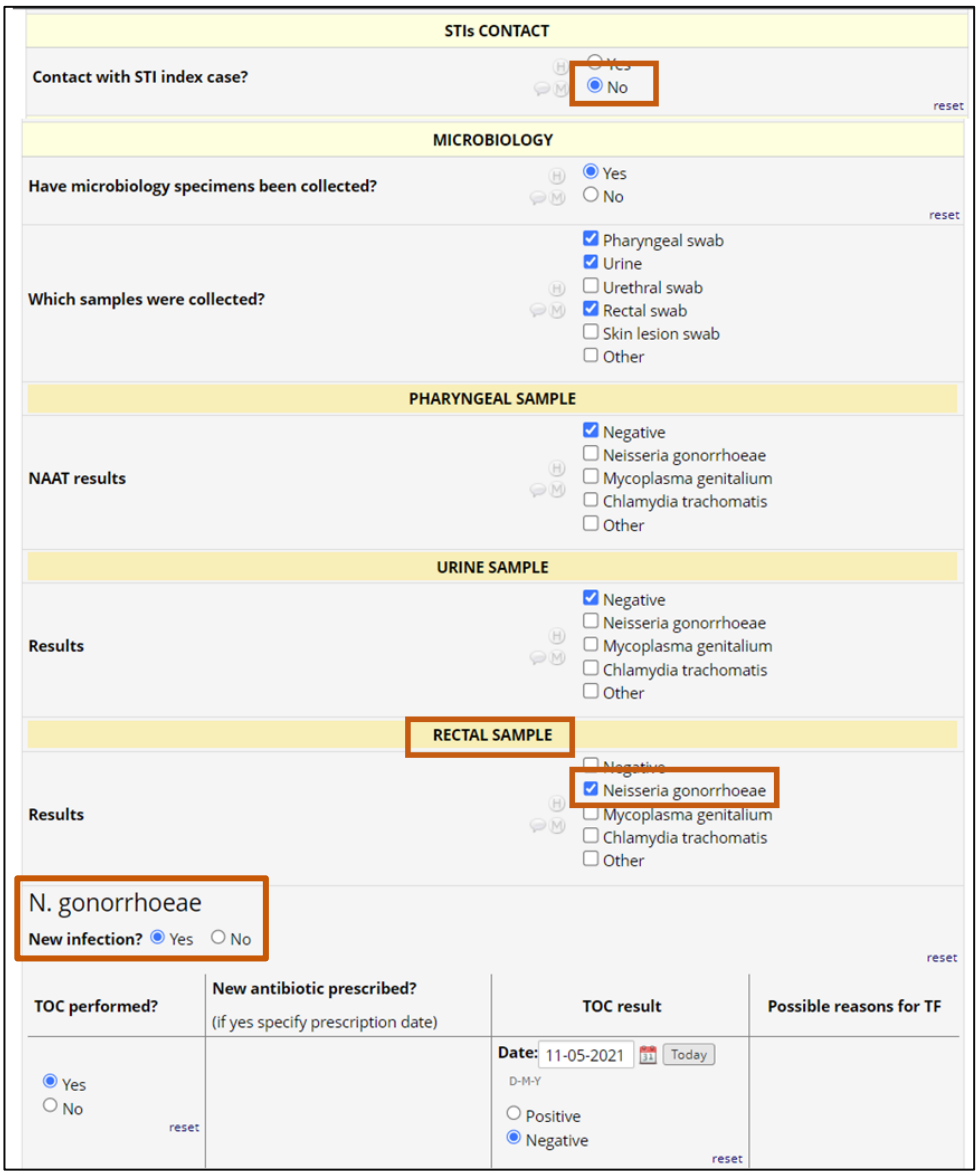
Likewise, the Antimicrobial Prescription instrument has been repeated 4-time, indicating that the patient had received targeted antibiotic treatment four times during the PrEP follow-up period.

A practical example

A hypothetical PrEP-user accessed Centro MISTRA for regular follow-up on 18-02-2021. After having linked patient name with the respective record ID in REDCap, the clinician opened a new Standard Visit instrument (T28) and started the clinical evaluation in parallel with the real-time data collection, **Figure 7**.

Figure 7. Content of standard visit instrument (partially reported)





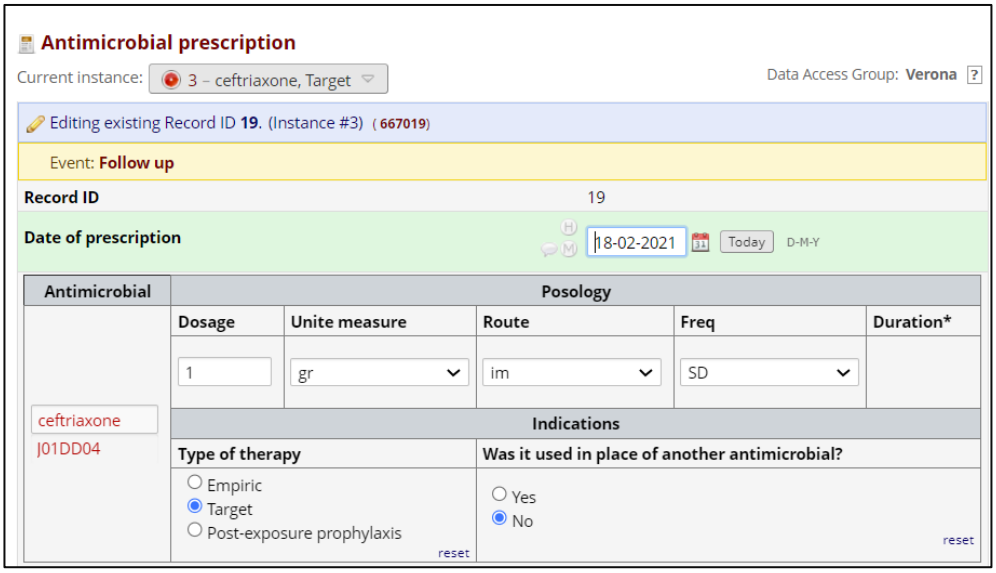
The clinical evaluation revealed that the patient did not claim STI signs & symptoms, he reported to have had MSM sexual intercourse, with 12 non-steady partners, two of them with HIV infection regularly assuming antiretroviral treatment. No contacts with STI case index have been reported. PrEP was taken with 100% compliance without adverse events.

In accordance with the clinical history and the evaluation performed by the clinician, the patient underwent a series of microbiological exams within the

usual PrEP screening (blood and urine samples, pharyngeal and rectal swabs). The microbiological results showed the detection of *Neisseria gonorrhoeae* in the rectal swab. The patient was diagnosed with gonococcal asymptomatic extra-genital infection.

Once the diagnosis has been made, the patient received the proper treatment. Details on the type of molecule, dosing, and length are reported in the Antimicrobial Prescription instrument (**Figure 8**), which is directly linked with the related standard visit instrument. The patient received ceftriaxone 1 gr single shot intramuscularly as targeted treatment.

Figure 8. Antimicrobial prescription instrument



To confirm the efficacy of treatment, a Test of Cure was performed on 11.05.2021 and resulted negative, indicating the microbiological eradication in the targeted site, **Figure 7** (page 49).

This is a small example of the applicability of the tool. However, this example clearly highlights the main advantages of this eCRF. The dashboard is extremely user-friendly, and the data workflow is intuitive, which

facilitate the data entry concomitantly minimising the risk of errors. The order of the variables to be entered within the tool was arranged by having in mind the usual course of an HIV-STIs visit, underlying how research and clinical perspectives were kept into account when developing the tool. The integration between clinical and research purposes represents the real innovative key-aspect of this tool which incredibly broadens the potential areas of applicability in both fields. The potential application areas of the tool will be described in the discussion section.

IMPLEMENTATION STUDY

After the development and piloting phases of the eCRF, the implementation study had the primary aim to test the usability of the tool by assessing the data import process and data processing (planning of exploratory analyses). As data reconciliation process, a further phase of verification of records during the data migration occurred. In this phase, target data were compared with source information to provide that the migration structure was assigning data. After generating specific rules, data from the original source dataset (Excel datasheet) were imported into the eCRF using the REDCap data import tool, which allowed the upload with subsequent automatic validation of data. This process was very linear and approximately 95% of data was successfully imported with no need of further review. The manual cleaning was requested for the remaining 5% of data, mostly targeting missing data. The well-conducted reconciliation process enabled a quality and rapid import of data, which were readily available for data analysis and processing. As further validation phase, exploratory analyses were conducted to test the extent of usability and feasibility of data. The pilot analysis focused on the assessment of COVID-19 impact the impact on PrEP users which accessed Centro MISTRA.

Statistical analysis of data entry system piloting

Descriptive analyses were performed. Outcomes were assessed and compared according to the following pre-selected timeframes within the study period*: i)* 1st January 2018- 24th February 2020 (pre-pandemic period); *ii)* 25th February 2020- 25th April 2021 (pandemic period, when two lockdown periods occurred and strong restriction measures were put in place); *iii)* 26th April 2021- 31st December 2022 (post-pandemic period, when no strong restrictive measures were adopted). These periods reflected the COVID-19 pandemic waves and the degree of preventive measures implementation in Italy. As inclusion criterion for this pilot study, patients on active PrEP with at least two consecutive visits was considered for analysis. PrEP discontinuation was defined as having no visits for more than 6 months. STI diagnosis was defined as one positive test at any site for at least one of the target pathogens. Infection caused by *Neisseria gonorrhoeae, Chlamydia trachomatis,* and *Mycoplasma genitalium* was diagnosed using multiple nucleic acid amplification testing (NAAT) assay, able to simultaneously detect and amplify bacterial DNA of all three pathogens (Seegene®, South Korea). Infection caused by *Treponema pallidum* (syphilis) was diagnosed using blood serology test.

Categorical variables were expressed as frequencies and percentages, while continuous variables were expressed as means and standard deviations (SD) or medians and quartiles (Q_1: 25th percentile and Q_3:75th percentile) according to the normal or nonnormal distribution of the variables. When feasible, *p value* was computed using non-parametric tests. Given the exploratory nature of the analysis, no sample size has been computed. All analyses were conducted using R (version 4.2.2, R core team 2022).

The analysis focused on evaluating, across pre-pandemic, pandemic, and post-pandemic periods, the distribution of PrEP users, the distribution of visits, the prevalence of bacterial STIs (*Treponema pallidum*, *Mycoplasma*

genitalium, Chlamydia trachomatis, Neisseria gonorrhoeae), and potential changes in scheme of PrEP use (daily, on-demand, discontinuation).

Data presentation

Within the period January 2018- September 2022, the eCRF hosted overall 311 patients accessing Centro MISTRA for PrEP evaluation and a total of 1696 visits. Fifty-five patients, accounting for 101 visits, did not meet the inclusion criterion and therefore were excluded from analysis.

Two hundred and fifty-six patients (accounting for 1595 visits, average 6.23 v/p) represented the final pool of patients for analysis. The mean age of patients at PrEP initiation was 37.8 years (SD 9.9). Patients initiating PrEP aged mostly between the ranges 30-39 and 40-49 years (94 patients, 37% and 78 patients, 30%). The yearly proportion of patients which started PrEP was higher in 2021 (38%), compared to other years, **Table 2** (page 55). All PrEP users were MSM. During the observation period, 744 rectal swabs, 687 pharyngeal swabs, 676 urine samples, and 1251 blood samples were collected for testing from the 256 patients during the scheduled visits. A total of 263 samples were tested positive: 80 for *Neisseria gonorrhoeae,* 80 for *Chlamydia trachomatis,* 59 for *Mycoplasma genitalium*, and 44 for *Treponema pallidum,* **Table 3** (page 56).

The testing volume across rectal, urogenital, and pharyngeal sites was similar, so that the frequency of infection (*N. gonorroheae* and/or *C. trachomatis* and/or *M. genitalium)* by anatomical site was computed. The proportion of STIs diagnosed on rectal site (136/744, 18%) was significantly higher ($p < 0.001$) in comparison with pharyngeal (46/687, 7%) and urogenital (37/676, 6%) sites. All infections occurred in asymptomatic individuals.

Table 2. Characteristics of PrEP users

SOCIO-DEMOGRAPHICS CHARACTERISTICS	
Age at PrEP initiation, years	
Mean (SD)	37.8 (9.9)
Median (Q1-Q3)	37.0 (30-44)
18-29 years	53 (21%)
30-39	94 (37%)
40-49	78 (30%)
≥ 50	31 (12%)
Year of PrEP initiation, n (%)	
2018	35 (14%)
2019	21 (8%)
2020	55 (21%)
2021	97 (38%)
2022	48 (19%)
SEXUAL BEHAVIOUR	
N° of non-steady partners, median (Q1-Q3)	8 (4-20)
Chemsex, n (%)	115 (45%)
Alcohol use, n (%)	242 (94%)
Alcohol binge, n (%)	33 (13%)
Alcohol Use Disorders Identification Test (AUDIT-C) was used for alcohol binge definition (≥ 3 points for female, ≥ 4 points for male).	

This finding is in line with literature data. Several studies have described similar STIs proportions at extra-genital sites in MSM PrEP users and among MSM population seeking medical care, with most of infections presenting asymptomatically (92,93). Our findings then pointed out the importance of multi-site active screening to improve the diagnostic sensitivity among high-risk populations and therefore promptly act in terms of patient treatment and partners notification.

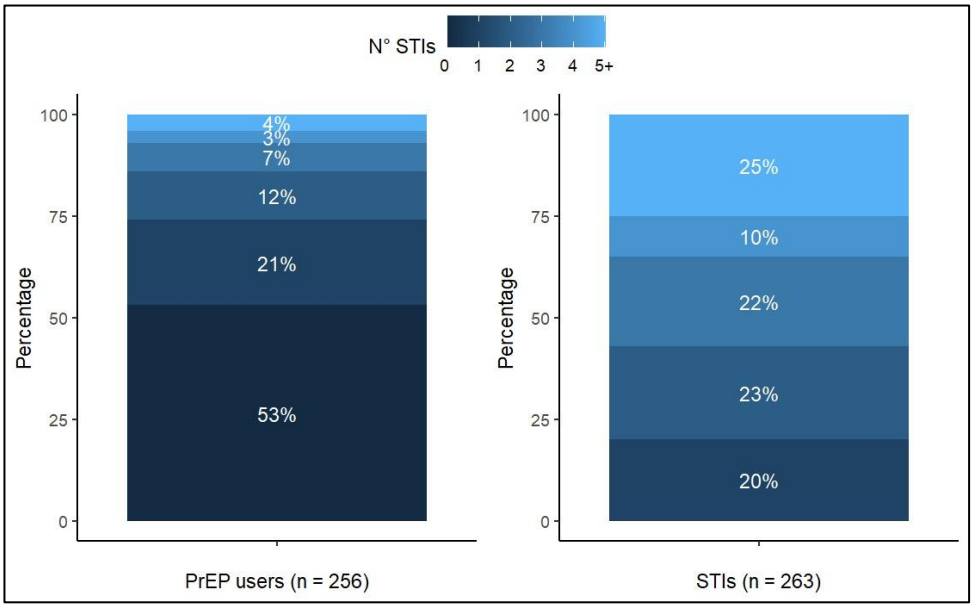
Table 3. Distribution of STIs diagnoses overall, by causative pathogen and infection site

Causative pathogen	Infection site	N° positive samples
Neisseria gonorroheae (Individuals diagnosed =58)	Rectal	35
	Pharyngeal	36
	Urine	9
	Total	**80**
Chlamydia trachomatis (Individuals diagnosed =60)	Rectal	56
	Pharyngeal	8
	Urine	16
	Total	**80**
Mycoplasma genitalium (Individuals diagnosed =48)	Rectal	45
	Pharyngeal	2
	Urine	12
	Total	**59**
Treponema pallidum (Individuals diagnosed=38)	**NA**	**44**
Total positive samples		**263**

When analysing the number and the distribution of all STIs diagnoses by PrEP users across the study period, 137 (53%) of patients were not diagnosed with any STIs; 53 (20%) patients were diagnosed with one STI, which accounted for 53 (21%) of all STIs infections diagnosed. A small proportion of PrEP users (7, 3%) were diagnosed with four STIs accounting for 28 (10%) of all STIs diagnosed. Ten (4%) of patients were diagnosed with five or more STIs, accounting for 65 (25%) of all STIs diagnosed, **Figure 9** (page 57).

The figure clearly depicts that one fourth of the diagnosed STIs is sustained by only ten PrEP users. As expected, these patients had a higher mean number of visits compared to the PrEP users diagnosed with fewer infections, indicating that the increased number of STIs is partly related to the longer follow-up, which translated to an increase of testing frequency and therefore of STIs diagnosis (data not shown).

Figure 9. Number of bacterial STI diagnoses per participant during the PrEP use and distribution of all bacterial STIs diagnoses (colour code applied).



The relatively small amount of data and events populating the tool limits the analysis that can be conducted. Therefore, no further analyses were performed to characterize the patients with multiple STIs diagnoses in a longitudinal way. Such approach could allow, for example, the computation of infection incidence as well as an examination of sexual behaviour, which usually has a dynamic and changeable pattern over time and therefore not suitable for cross-sectional analysis.

After a general description of the cohort, comparative analyses were then planned to assess the distribution of PrEP visits and patients across three pre-selected periods, **Table 4** (page 59) and **Table 5** (page 60). A total of 68 (26%), 64 (25%), and 124 (49%) patients in pre-pandemic, pandemic, and post-pandemic periods underwent the first PrEP visit. The total number of patients lost to follow-up were 45 (18%) across the whole study period. Adjusting for the total number of patients evaluated in each time period, the proportion of patients lost to follow-up gradually decreased across periods

(pre-pandemic: 16/68, 23%, pandemic: 12/114, 10%, post-pandemic: 17/228, 7%). This result was likely related to the decreased lockdown measures over time.

As far as PrEP initiation scheme is concerned, 105 (41%) patients chose PrEP on-demand, while 151 (49%) patients chose the daily regimen. The proportion of patients initiating daily or on-demand scheme was similar across the three periods. One hundred and ninety-two (75%) patients retained same PrEP scheme over time: 129 patients (67%) who started PrEP on-demand and 63 patients (33%) who started daily scheme. Sixty four out of 256 patients (25%) reported at least one switch of PrEP scheme during the study period.

In order to quantify the possible impact of COVID-19 restrictions on accesses to Centro MISTRA, a further analysis was conducted using the event visit as unit of analysis (n=1595 visits). The total number of PrEP visits in each period was compared to the expected visits which should have occurred during the same time-period for the same number of patients in a normal clinical scenario. The most significant difference ($p < 0.05$) between conducted and expected visits was reported for the pandemic period (362/463, 78%) compared to the other periods, for which the difference was much less marked (pre-pandemic: 287/303, 95% and post-pandemic: 946/971, 97%). Together with the decline of number of visits, an increased time between visits was also reported. During the pandemic period, the mean time between visits was on average longer (3.3 months, SD 2.0) compared to those computed in the other periods. These data, despite based on a small sample size, suggested a general reduction in accessing HIV-STIs services by PrEP users.

Similar analysis was carried out for evaluating the PrEP scheme distribution across the three time-periods, **Table 5** (page 60), **Figure 10** (page 61).

Table 4. Distribution of PrEP users, PrEP visits (events), and STIs diagnoses across the pre-pandemic, pandemic, and post-pandemic periods

	PERIODS			Total
	Pre-pandemic	**Pandemic**	**Post-pandemic**	
PATIENTS' DATA				
N° of evaluated patients for PrEP 1st visit	68 (26%)	64 (25%)	124 (49%)	**256**
N° of evaluated patients overall (patients undergoing 1st visit or follow-up visit)	68 (17%)	114 (28%)	228 (55%)°	410
N° of patients lost to follow-up	16 (35%)	12 (26%)	17 (39%)	45
N° of loss of follow-up, n* / **N° of evaluated patients**	16/68	12/114	17/228	45/410
Proportion %	23%	10%	7%	11%
PrEP initiation scheme				
Daily	23 (22%)	26 (24%)	56 (54%)	105
On demand	33 (22%)	31 (21%)	87 (57%)	151
Total	56 (22%)	57 (23%)	143 (55%)	**256**
VISITS DATA				
N° of conducted visits,* n / **N° of expected visits**	287/303	362/463	946/971	1595/1737
Proportion, %	95%	78%	97%	92%
Mean-time between visits (months, SD)	2.2.9 (0.9)	3.3 (2.0)	3.0 (1.1)	3.1 (1.7)
Median time between visits (months, Q1-Q2)	2.7 (2.4-3.4)	2.9 (2.5-3-5)	3.0 (2.3-3.5)	2.9 (2.6-3.4)
STIs DATA				
Any STI	32 (12%)	63 (24%)	168 (64%)	**263**
Neisseria gonorrhoeae	12 (15%)	13 (16%)	55 (69%)	80
Chlamydia trachomatis	9 (11%)	21 (26%)	50 (63%)	80
Mycoplasma genitalium	6 (10%)	19 (33%)	34 (57%)	59
Treponema pallidum	5 (12%)	10 (22%)	29 (66%)	44

N° of conducted visits: Initial PrEP visits (before PrEP prescription) + PrEP follow-up visits (after PrEP prescription). N° of expected visits: estimated number of visits computed considering the patient entry point and the timeframe. Mean/median time: weighted mean/median time by the number of patient-level visits.

° Two patients with loss of follow-up in the pandemic period, were again linked to care in the post-pandemic period

**P value < 0.05*

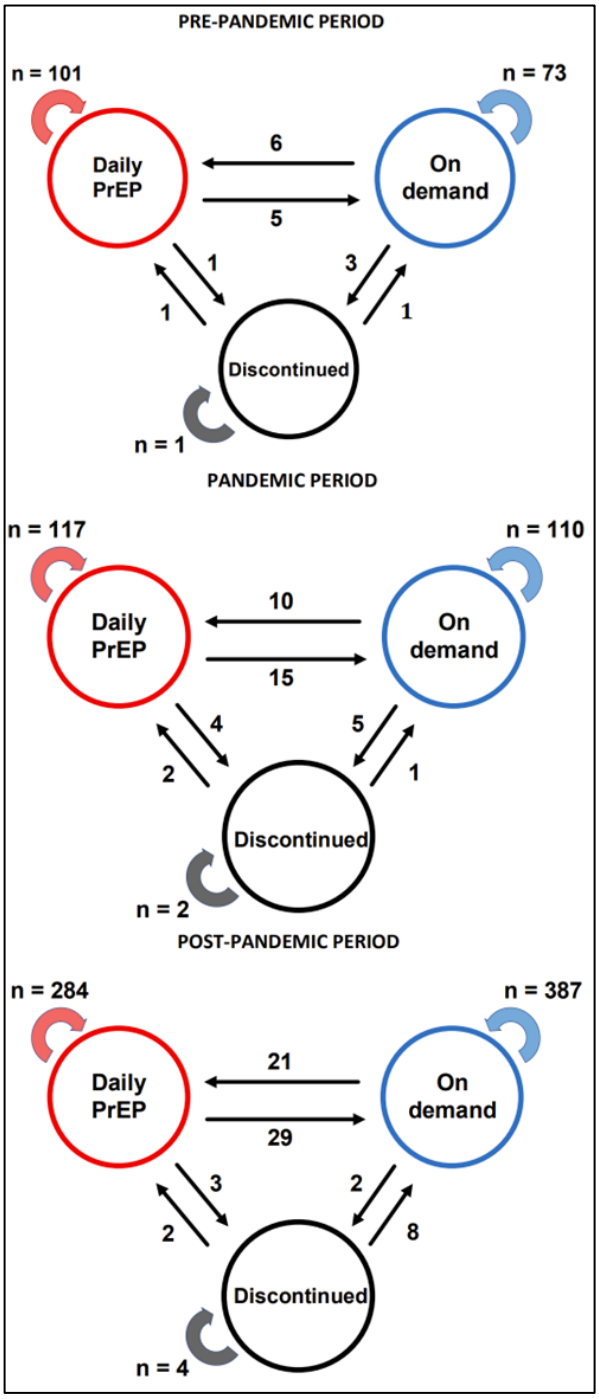
Table 5. Distribution of PrEP intake scheme by visit (event) across the pre-pandemic, pandemic, and post-pandemic periods

PrEP scheme	PERIODS			Total
	Pre-pandemic	Pandemic	Post pandemic	
Daily	107 (19%)	129 (24%)	307 (57%)	543
On-demand	80 (12%)	126 (20%)	424 (68%)	630
Discontinuation	5 (20%)	11 (44%)	9 (36%)	25
Total of visits°	**192 (16%)**	**266 (22%)**	**740 (62%)**	**1198**

°The denominator is represented exclusively by the PrEP follow-up visits (after PrEP prescription)

Compared to the total number of visits conducted within the study period, the change of PrEP scheme was a relatively rare event. Regimen change, in fact, was registered overall in 119 out of 1198 follow-up visits (10%). When grouping by period, 17/192 (8.8%), 37/266 (14%), and 65/740 (9%) changes were reported in pre-pandemic, pandemic, and post-pandemic periods, respectively. A total of 25 PrEP discontinuation events were reported overall. Transitions between PrEP schemes from on-demand to daily PrEP and from daily PrEP to on-demand PrEP separately and from either PrEP regimen to discontinuation for every period are represented in **Figure 10** (page 61). Focusing on pandemic period (266 visits, 69 patients), changes were reported in 37 (14%) visits. Switches from daily to on-demand scheme was more frequent than the opposite (15 *versus* 10 events). PrEP discontinuation was more frequently registered in the pandemic period (11 out of 25 events), compared to the pre- and post-pandemic ones. However, our data revealed that PrEP scheme modification was in general uncommon. Some changes have been observed during the pandemic period, mainly switching from daily to on/demand or to discontinuation, indicating probably a reduced need of PrEP due to sexual behaviour change or, alternatively, to a difficulty encountered in accessing the clinic linked to the lockdown restrictions.

Figure 10: Transitions (black arrows) between PrEP schemes (daily and on-demand) and from each scheme to discontinuation



Number of patients undergoing a change of PrEP scheme: pre-pandemic period n=46, pandemic period: n= 69; post-pandemic period n=182

DISCUSSION

This ancillary study of the WHO SRH project led to the development, validation, and implementation at UHVR of an electronic data capture tool, on the REDCap platform, hosting standardised and homogeneous HIV-STIs and behavioural data. The tool allows data collection, data management, data download, and data analysis with strict IT security controls in a very cost and time efficient manner. The intuitive workflow and multiple quality checks both for data and drug prescription embedded in the system allow a rapid and real-time data collection with a reduced probability of data entry errors. Whilst the tool was structured primarily for research purposes, clinical perspectives were taken into account during its development and validation. The tool is multi-faceted and can have a wide range of applicability and great potential in addressing issues in several fields. The implementation study was conducted for both testing the usability of the tool and setting up exploratory analyses as further data validation process.

Routine healthcare and research have been profoundly influenced by digital technologies (94). Prior to COVID-19, there was much unexplored potential in the use of electronic tools worldwide (95). The availability of timely and high-quality evidence has become mandatory during the COVID-19 pandemic, due to the need of promptly addressing clinical questions, informing decision making for stakeholders and policy makers, and supporting healthcare service provision. Most countries have established and implemented digital tools and platforms to collect and share data and information about COVID-19, in the attempt of facing the pandemic in a scientific way.

It was in this context that the idea of developing an electronic collection tool of HIV-STIs data has taken shape. Several worldwide reports from the literature described a severe impact of COVID-19 on sexual health. However, the available evidence is mostly limited to qualitative study design

with poor multi-sites comparison validity. The tool was conceptualised for having a very broad range of applicability in both research and clinical contexts. The starting point of the tool versatility is the collection of data derived from routine clinical practice, which underwent a systematic process of standardisation and validation.

The longitudinal structure of the tool based on modules strongly facilitates the data entry, that can be performed not only by the data clerks but also by clinicians real-time during the patient consultation with very little burden. The tool is intended to serve also as health support for a general improvement of clinical practice. Clinicians may, in fact, benefit from regular reports generated by REDCap with focus on specific clinical questions.

The tool modularity can facilitate the implementation of telehealth service provision allowing also the self-administration of specific data collection modules (*e.g.,* sexual behaviour or PrEP intake) through MyCap, a participant-facing mobile application used for automated administration of active tasks. All data collected in the app are automatically sent back to the REDCap server in a completely secured way. This approach would allow off-site patients to complete their self-assessment while simultaneously enabling the clinicians to receive data in advance and optimise the time of consultation (74,96).

This functionality appears to be of particular importance in the modern era where telehealth is strongly encouraged, particularly during the pandemics (like the recent COVID-19 one), but also as alternative sustainable cost-effective way to provide care, which in turn may reduce potential provider-patient supply-demand mismatch (97).

The tool has multiple applications also in the research context. The longitudinal structure allows to easily store, update data from same centre, and rapidly incorporate new real-world data from other centres, which are suitable for the conduction of a wide range of implementation studies to

address specific key-questions or filling some knowledge gaps (98, 99). The tool is structured in a way, in fact, that the data collection burden is minimised in favour of a rapid generation of high-quality outputs, which can timely and efficiently guide clinical decision making and real-time inform stakeholders and public policy makers.

To test the tool's usability, a pilot study assessing the COVID-19 impact on PrEP users accessing Centro MISTRA was conducted, as small but pragmatic example on implementation research. The exploratory analysis beyond testing the data processing, provided some interesting results which act as valid script for future research. Furthermore, the findings underlined the pivotal role of high-quality longitudinal data in clinical research, which allows to explore dynamic rather than static concepts, and therefore to detect potential patterns of changes of variables measured over time in a selected population at both individual and group-level. When applying this concept into the STIs field, it becomes automatically clear how important would be the longitudinal assessment of sexual behaviour, which can be very changeable, as well as the PrEP use habits (100). The tool is currently populated with a small amount of single-centre patient data and the added value of longitudinal studies cannot be at the moment fully exploited. However, in the future, when the tool will acquire new events as well as new patients' data also from other international HIV-STIs centres, the potential of analysis as well as the related outputs will enormously increase together with the performance of the tool.

The research infrastructure with its potential limitless possibility of hosting longitudinal data can act as a platform suitable for the implementation of perpetual observational studies (POS). A POS is a prospective, observational clinical study enrolling patients on a perpetual basis. POS creates a clinical research backbone, ready to concurrently or sequentially embed studies (observational, experimental, investigator-initiated, or commercial), and efficiently advance the evidence base for infectious diseases management

(101). A well-established example of research network is the European Clinical Research Alliance on Infectious Diseases (ECRAID, https://www.ecraid.eu/) clinical research network, which currently is implementing five POS.

The eCRF functionality can also be applied for surveillance purposes, for regularly tracking the STIs cases. The tool might serve as sexual health database collecting real-time epidemiological information from hospitals and laboratories at local or regional level.

The present tool has some limitations mainly related to the lack of external validation. Several interventions are planned in the future to improve the solidity and the applicability of the tool. First, an external piloting and validation phase aimed at assessing performance using novel data is scheduled in selected international centres, with different income and capability (*e.g.,* lower income countries). Second, agreements on ethical level are currently developing for an upcoming implementation at UOB. Potential further target centres for validation will be suggested with the mediation of the WHO.

CONCLUSIONS

This study described the development steps and the current and future potential applications of an electronic tool for HIV-STIs data collection. Despite still in the early stages, the tool is valuable to face potential future health emergencies, being able to timely answer clinical and research questions to inform clinical decision making and stakeholders public health actions. The tool can also serve as healthcare support with telehealth approach to ensure care *continuum*.

With targeted ameliorative interventions and the constant population with data, the eCRF has the purpose of becoming a well-established internationally recognised platform hosting standardised, homogeneous, longitudinal HIV-STIs data from different centres to promote implementation studies, as part of an HIV-STIs integrated international research network.

ACKNOWLEDGEMENTS

Four months after the start of my PhD course, the COVID-19 pandemic devastatingly came into people's life, including mine, and totally subverted the original idea I had in mind on my PhD project. The change of topic, initially seen as unfortunate and forced episode, turned out to be one of the most fruitful individual experiences I have had so far. I hope that this work would be considered as a little but clear example of how much can be achieved through active participation and multidisciplinary collaboration, despite all the difficulties encountered during the pandemic.

For this reason, I am deeply grateful to the entire team for its essential contribution to this project. This work would not have been possible without the efforts of every single component of the team.

My biggest thanks go to Professor Evelina Tacconelli for her scientific advice and sincere cooperation in every step of the project.

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REFERENCES

1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020.

2. Wu D, Wu T, Liu Q, Yang Z. The SARS-CoV-2 outbreak: What we know. *Int J Infect Dis.* 2020 May;94:44–8.

3. Wang Q, Qu Z, Tu S, Chen X, Hou Z. The whole-of-society approach of mass COVID-19 vaccination in China: a qualitative study. *Health Res Policy* Syst. 2022 Dec 30;20(1):142.

4. Moradian N, Ochs HD, Sedikies C, Hamblin MR, Camargo CA, Martinez JA, *et al.* The urgent need for integrated science to fight COVID-19 pandemic and beyond. *J Transl Med.* 2020 Dec;18(1):205.

5. World Health Organization. COVID-19 Strategic Preparedness and Response Plan 2022: Global Monitoring and Evaluation Framework [Internet]. 2022. Available from: https://www.who.int/publications/m/item/covid-19-strategic-preparedness-and-response-plan-2022--global-monitoring-and-evaluation-framework

6. Centers for Disease Control and Prevention. CDC Strategy for Global Response to COVID-19 (2020-2023) [Internet]. 2022. Available from: https://www.cdc.gov/coronavirus/2019-ncov/global-covid-19/global-response-strategy.html

7. Marinus R, Mofid S, Mpandzou M, Kühler TC. Rolling Reviews During COVID-19: The European Union Experience in a Global Context. *Clin Ther.* 2022 Mar;44(3):352–63.

8. Cassidy C, Dever D, Stanbery L, Edelman G, Dworkin L, Nemunaitis J. FDA efficiency for approval process of COVID-19 therapeutics. *Infect Agent Cancer*. 2020 Dec;15(1):73.

9. Perra N. Non-pharmaceutical interventions during the COVID-19 pandemic: A review. *Phys Rep*. 2021 May;913:1–52.

10. World Health Organization. WHO Coronavirus (COVID-19) Dashboard [Internet]. Available from: https://covid19.who.int/

11. OCDE- Better Policies for Better Life. The health impact of COVID-19 [Internet]. Available from: oecd-ilibrary.org/sites/b0118fae-en/index.html?itemId=/content/component/b0118fae-en

12. Assefa Y, Gilks CF, Reid S, van de Pas R, Gete DG, Van Damme W. Analysis of the COVID-19 pandemic: lessons towards a more effective response to public health emergencies. *Glob Health.* 2022 Feb 4;18(1):10.

13. Msemburi W, Karlinsky A, Knutson V, Aleshin-Guendel S, Chatterji S, Wakefield J. The WHO estimates of excess mortality associated with the COVID-19 pandemic. *Nature*. 2022 Dec 14

14. Wang H, Paulson KR, Pease SA, Watson S, Comfort H, Zheng P, *et al.* Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21. *The Lancet.* 2022 Apr;399(10334):1513–36.

15. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, *et al.* Post-acute COVID-19 syndrome. *Nat Med.* 2021 Apr;27(4):601–15.

16. A clinical case definition of post COVID-19 condition by a Delphi consensus [Internet]. 2021. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1

17. O'Mahoney LL, Routen A, Gillies C, Ekezie W, Welford A, Zhang A, *et al.* The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. *eClinicalMedicine*. 2023 Jan;55:101762.

18. Wise J. Long covid: WHO calls on countries to offer patients more rehabilitation. *BMJ*. 2021 Feb 10;n405.

19. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, *et al.* More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis [Internet]. Infectious Diseases

(except HIV/AIDS); 2021 Jan [cited 2023 Jan 3]. Available from: http://medrxiv.org/lookup/doi/10.1101/2021.01.27.21250617

20. Moreno-Pérez O, Merino E, Leon-Ramirez JM, Andres M, Ramos JM, Arenas-Jiménez J, *et al.* Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. *J Infect*. 2021 Mar;82(3):378–83.

21. Michelen M, Manoharan L, Elkheir N, Cheng V, Dagens A, Hastie C, *et al*. Characterising long COVID: a living systematic review. *BMJ Glob Health.* 2021 Sep;6(9):e005427.

22. Malik P, Patel K, Pinto C, Jaiswal R, Tirupathi R, Pillai S, *et al.* Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)—A systematic review and meta-analysis. *J Med Virol.* 2022 Jan;94(1):253–62.

23. World Health Organization. Third round of the global pulse survey on continuity of essential health services during the COVID-19 pandemic [Internet]. 2022. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-EHS_continuity-survey-2022.1

24. Lee WE, Park SW, Weinberger DM, Olson D, Simonsen L, Grenfell BT, *et al.* Direct and indirect mortality impacts of the COVID-19 pandemic in the US, March 2020- April 2021. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.02.10.22270721

25. Sabetkish N, Rahmani A. The overall impact of COVID -19 on healthcare during the pandemic: A multidisciplinary point of view. *Health Sci Rep*. 2021 Dec

26. Gralnek IM, Hassan C, Dinis-Ribeiro M. COVID-19 and endoscopy: implications for healthcare and digestive cancer screening. *Nat Rev Gastroenterol Hepatol.* 2020 Aug;17(8):444–6.

27. Hanna TP, King WD, Thibodeau S, Jalink M, Paulin GA, Harvey-Jones E, *et al.* Mortality due to cancer treatment delay: systematic review and meta-analysis. *BMJ.* 2020 Nov 4;m4087.

28. Sokolski M, Gajewski P, Zymliński R, Biegus J, Berg JMT, Bor W, *et al.* Impact of Coronavirus Disease 2019 (COVID-19) Outbreak on Acute Admissions at the Emergency and Cardiology Departments Across Europe. Am J Med. 2021 Apr;134(4):482–9.

29. International Conference on Population and Development– ICPD (1994). Program of Action, 1994. Available from: https://www.un.org/en/development/desa/population/migration/generalassembly/docs/globalcompact/A_CONF.171_13.pdf

30. World Health Organization. Sexual and Reproductive Health and Research (SRH). Available from: https://www.who.int/teams/sexual-and-reproductive-health-and-research/key-areas-of-work/sexual-health/defining-sexual-health

31. United Nations Population Fund. Sexual & Reproductive Health-A life Cicle Approach. Available from: https://www.unfpa.org/sexual-reproductive-health#readmore-expand

32. Tang K, Gaoshan J, Ahonsi B, Ali M, Bonet M, Broutet N, *et al.* Sexual and reproductive health (SRH): a key issue in the emergency response to the coronavirus disease (COVID- 19) outbreak. *Reprod Health.* 2020 Dec;17(1):59.

33. A joint report by EPF & IPPF EN. Sexual and Reproductive Health and Rights during the COVID-19 pandemic. 2020. Available from: https://www.epfweb.org/sites/default/files/2020-05/epf_-_ipff_en_joint_report_sexual_and_reproductive_health_during_the_covid-19_pandemic_23.04.2020.pdf

34. Kouanda S, Nahyuha Chomi E, Kim C, Jen S, Bahamondes L, Cecatti JG, *et al.* Health systems analysis and evaluation of the barriers to availability, utilisation and readiness of sexual and reproductive health services in COVID-19-affected areas: a WHO mixed-methods study protocol. *BMJ Open*. 2022 Jun;12(6):e057810.

35. World Health Organization. Operational guidance for maintaining essential health services during an outbreak, 2020. Available from: https://apps.who.int/iris/bitstream/handle/10665/331561/WHO-2019-nCoV-essential_health_services-2020.1eng.pdf?sequence=1&isAllowed=y
36. UNFPA. Impact of the COVID-19 Pandemic on Family Planning and Ending Gender-based Violence, Female Genital Mutilation and Child Marriage [Internet]. 2020. Available from: https://www.unfpa.org/resources/impact-covid-19-pandemic-family-planning-and-ending-gender-based-violence-female-genital
37. Riley, Sully, Ahmed, Biddlecom. Estimates of the Potential Impact of the COVID-19 Pandemic on Sexual and Reproductive Health In Low- and Middle-Income Countries. *Int Perspect Sex Reprod Health.* 2020;46:73.
38. Fulcher IR, Onwuzurike C, Goldberg AB, Cottrill AA, Fortin J, Janiak E. The impact of the COVID-19 pandemic on abortion care utilization and disparities by age. *Am J Obstet Gynecol*. 2022 Jun;226(6):819.e1-819.e15.
39. Martin Andersen. COVID-19 Surgical Abortion Restriction Did Not Reduce Visits to Abortion Clinics, 2020. Available from: https://docs.iza.org/dp13832.pdf
40. UNICEF. Direct and indirect effects of the COVID-19 pandemic and response in South Asia, 2021. Available from: https://www.unicef.org/rosa/media/13066/file/Main%20Report.pdf
41. Vora KS, Saiyed S, Natesan S. Impact of COVID-19 on family planning services in India*. Sex Reprod Health Matters*. 2020 Jan 1;28(1):1785378.
42. Fernanda Marquez-Padilla and Biani Saavedra. COVID-19 and (Un)Desired Fertility: The Effect of Stay-at-Home Orders on Abortions in Mexico City. *J Popul Econ*. 2022;35(1):269-305
43. MSI Reproductive Choices. Press release: 1.9m clients lost access to our services due to COVID-19, 2020. Available from: https://www.msichoices.org/news-and-insights/news/2020/8/press-release-19m-clients-lost-access-to-our-services-due-to-covid-19/

44. Walker SH. Effect of the COVID-19 pandemic on contraceptive prescribing in general practice: a retrospective analysis of English prescribing data between 2019 and 2020. *Contracept Reprod Med*. 2022 Dec;7(1):3.

45. Rutgers - For Sexual and reproductive Health and Rights. I feel that things are out of my hand [Internet]. 2020. Available from: https://rutgers.international/wp-content/uploads/2021/09/Rutgers-SRHR-COVID-19-Report_International-Study.pdf

46. PMA Agile/Gender & International Centre for Reproductive Health-Kenya (ICRHK). Gender & covid-19: access to health and contraception, 2020. Available from: https://www.pmadata.org/sites/default/files/data_product_results/PMA%20Gender%20COVID%20Access%20Health%20Contraception%202020_0.pdf

47. United Nations. States must combat domestic violence in the context of COVID-19 lockdowns – UN rights expert, 2020. Available from: https://www.ohchr.org/en/press-releases/2020/03/states-must-combat-domestic-violence-context-covid-19-lockdowns-un-rights

48. UN women. Measuring the shadow pandemic: Violence against women during COVID-19, Available from: https://data.unwomen.org/publications/vaw-rga

49. UNFPA E. Gender-Based Violence and COVID-19 Actions, Gaps and the Way Forward, 2022. Available from: https://esaro.unfpa.org/en/publications/gender-based-violence-and-covid-19

50. Human Rights Watch. Submission to the UN special rapporteur on violence against women, its causes and consequences regarding COVID-19 and the increase of domestic violence against women, 2020. Available from: https://www.hrw.org/news/2020/07/03/submission-un-special-rapporteur-violence-against-women-its-causes-and-consequences

51. Linnemayr S, Jennings Mayo-Wilson L, Saya U, Wagner Z, MacCarthy S, Walukaga S, *et al.* HIV Care Experiences During the COVID-19 Pandemic: Mixed-Methods Telephone Interviews with Clinic-Enrolled HIV-Infected Adults in Uganda. *AIDS Behav*. 2021 Jan;25(1):28–39.

52. Stephenson R, Chavanduka TMD, Rosso MT, Sullivan SP, Pitter RA, Hunter AS, *et al.* Sex in the Time of COVID-19: Results of an Online Survey of Gay, Bisexual and Other Men Who Have Sex with Men's Experience of Sex and HIV Prevention During the US COVID-19 Epidemic. *AIDS Behav.* 2021 Jan;25(1):40–8.

53. Howarth AR, Saunders J, Reid D, Kelly I, Wayal S, Weatherburn P*, et al.* 'Stay at home …': exploring the impact of the COVID-19 public health response on sexual behaviour and health service use among men who have sex with men: findings from a large online survey in the UK. *Sex Transm Infect*. 2022 Aug;98(5):346–52.

54. Chone JS, Lima SVMA, Fronteira I, Mendes IAC, Shaaban AN, Martins M do RO, *et al.* Factors associated with chemsex in Portugal during the COVID-19 pandemic. *Rev Lat Am Enfermagem.* 2021;29:e3474.

55. Nagendra G, Carnevale C, Neu N, Cohall A, Zucker J. The Potential Impact and Availability of Sexual Health Services During the COVID-19 Pandemic. *Sex Transm Dis*. 2020 Jul;47(7):434–6.

56. Santos GM, Ackerman B, Rao A, Wallach S, Ayala G, Lamontage E, *et al*. Economic, Mental Health, HIV Prevention and HIV Treatment Impacts of COVID-19 and the COVID-19 Response on a Global Sample of Cisgender Gay Men and Other Men Who Have Sex with Men. *AIDS Behav.* 2021 Feb;25(2):311–21.

57. Pinto CN, Niles JK, Kaufman HW, Marlowe EM, Alagia DP, Chi G, *et al.* Impact of the COVID-19 Pandemic on Chlamydia and Gonorrhea Screening in the U.S *Am J Prev Med*. 2021 Sep;61(3):386-393. doi: 10.1016/j.amepre.2021.03.009.

58. The impact of the COVID-19 pandemic on prevention, testing, diagnosis and care for sexually transmitted infections, HIV and viral hepatitis in England, 2020. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/943657/Impact_of_COVID-19_Report_2020.pdf

59. Darcis G, Vaira D, Moutschen M. Impact of coronavirus pandemic and containment measures on HIV diagnosis. Epidemiol Infect. 2020;148:e185.

60. Ojukwu E, Chan C, Ibitoye BM, Tawfik A, Nguyen Y, Omobhude F, et al. Impact of the COVID-19 pandemic on the HIV care continuum: a mixed-method systematic review protocol. JBI Evid Synth, 2022 21(1):223-229

61. Seyed Alinaghi SA, Mirzapour P, Pashaei Z, Afzalian A, Tantuoyir MM, Salmani R, *et al*. The impacts of COVID-19 pandemic on service delivery and treatment outcomes in people living with HIV: a systematic review. *AIDS Res Ther.* 2023 Jan 6;20(1):4.

62. CDC. COVID-19 disruptions in HIV testing and prevention highlight need for innovation and investment before the next public health emergency, 2022. Available from: https://www.cdc.gov/media/releases/2022/s1201-HIV-COVID-19.html#:~:text=HIV%20testing%20and%20prescriptions%20for,PrEP%20prescriptions%20fell%20about%206%25.

63. CDC. Impact of COVID-19 on STDs, 2022. Available from: https://www.cdc.gov/std/statistics/2020/impact.htm

64. Jenness SM, Le Guillou A, Chandra C, Mann LM, Sanchez T, Westreich D, *et al.* Projected HIV and Bacterial Sexually Transmitted Infection Incidence Following COVID-19–Related Sexual Distancing and Clinical Service Interruption. *J Infect Dis.* 2021 Mar 29;223(6):1019–28.

65. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, *et al.* Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. *N Engl J Med.* 2010 Dec 30;363(27):2587–99.

66. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, *et al.* Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. *N Engl J Med*. 2012 Aug 2;367(5):423–34.
67. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, *et al.* Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet.* 2013 Jun;381(9883):2083–90.
68. Pre-exposure prophylaxis (PrEP)- Global HIV Programme. Available from: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/prevention/pre-exposure-prophylaxis#:~:text=As%20of%20September%202015%2C%20WHO,as%20part%20of%20comprehensive%20prevention.
69. World Health Organization. WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection, 2017. Available from: https://www.who.int/tools/prep-implementation-tool
70. ECDC. HIV Pre-Exposure Prophylaxis in the EU/EEA and the UK: implementation, standards and monitoring - Operational guidance, 2021. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/HIV-Pre-Exposure-Prophylaxis-in-the-EU-EEA-UK.pdf
71. Hill BJ, Anderson B, Lock L. COVID-19 Pandemic, Pre-exposure Prophylaxis (PrEP) Care, and HIV/STI Testing Among Patients Receiving Care in Three HIV Epidemic Priority States. *AIDS and Behavior*. 2021 25:1361–1365
72. Hammoud MA, Grulich A, Holt M, Maher L, Murphy D, Jin F, *et al.* Substantial Decline in Use of HIV Preexposure Prophylaxis Following Introduction of COVID-19 Physical Distancing Restrictions in Australia: Results From a Prospective Observational Study of Gay and Bisexual Men. *J Acquir Immune Defic Syndr.* 2021 Jan 1;86(1):22–30.

73. Hyndman I, Nugent D, Whitlock GG, McOwan A, Girometti N. COVID-19 restrictions and changing sexual behaviours in HIV-negative MSM at high risk of HIV infection in London, UK. *Sex Transm Infect*. 2021 Nov;97(7):521–4.

74. Awowole IO, Ijarotimi OA. Restrictive abortion laws, COVID-19, telehealth, and medication abortion in the SDG era. *Lancet Glob Health*. 2022 Jan;10(1):e14–5.

75. Lindberg LD, Mueller J, Haas M, Jones RK. Telehealth for Contraceptive Care During the COVID-19 Pandemic: Results of a 2021 National Survey. *Am J Public Health*. 2022 Jun;112(S5):S545–54.

76. Saragih ID, Imanuel Tonapa S, Porta CM, Lee BO. Effects of telehealth interventions for adolescent sexual health: A systematic review and meta-analysis of randomized controlled studies. *J Telemed Telecare*. 2021 Dec 13;1357633X2110477.

77. World Health Organization. Implementing telemedicine services during COVID-19: guiding principles and considerations for a stepwise approach, 2021. Available from: https://apps.who.int/iris/handle/10665/336862

78. World Health Organization. Consolidated telemedicine implementation guide, 2022. Available from: https://www.who.int/publications/i/item/9789240059184

79. World Health Organization. SCORE for health data technical package: global report on health data systems and capacity, 2020. Available from: https://www.who.int/publications/i/item/9789240018709

80. Brown J, Bhatnagar M, Gordon H, Goodner J, Cobb JP, Lutrick K. An Electronic Data Capture Tool for Data Collection During Public Health Emergencies: Development and Usability Study. *JMIR Hum Factors*. 2022 Jun 9;9(2):e35032.

81. Brat GA, Weber GM, Gehlenborg N, Avillach P, Palmer NP, Chiovato L, *et al.* International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium. *Npj Digit Med*. 2020 Aug 19;3(1):109.

82. World Health Organization. The WHO Global Clinical Platform for COVID-19. Available from: https://www.who.int/teams/health-care-readiness/covid-19/data-platform#:~:text=In%20response%2C%20the%20WHO%20has,clinical%20characteristics%20of%20COVID%2D19

83. Stock SJ, Zoega H, Brockway M, Mulholland RH, Miller JE, Been JV, *et al.* The international Perinatal Outcomes in the Pandemic (iPOP) study: protocol. *Wellcome Open Res*. 2021 Feb 2;6:21.

84. Sialon II- capacity building in combining targeted prevention with meaningful HIV surveillance among MSM. Global AIDS Response Progress Reporting. Available from: https://webgate.ec.europa.eu/chafea_pdb/assets/files/pdb/20101211/20101211_d09-02_en_ps_garpr_indicators_reporting.pdf

85. Mirandola M, Gios L, Sherriff N, Marcus U, Toskin I, Rosinska M, et al. Quantifying unmet prevention needs among MSM in Europe through a multi-site bio-behavioural survey. *Euro Surveill*. 2018 Dec;23(49):1800097

86. World Health Organization. WHO releases new module of the PrEP implementation tool on integration of STI services. 2022. Available from: https://www.who.int/news/item/06-09-2022-new-module-prep-implementation-tool-on-integration-of-sti-services

87. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009 Apr;42(2):377–81.

88. Latha M, Bellary S, Krishnankutty B. Basics of case report form designing in clinical research. *Perspect Clin Res.* 2014;5(4):159.

89. Heywood A, Boone D U Measure Evaluation. Guidelines For Data Management Standards in Routine Health Information System, 2015. Available from: https://www.measureevaluation.org/resources/publications/ms-15-99.html

90. Brembilla A, Martin B, Parmentier AL, Desmarets M, Falcoz PE, Puyraveau M, *et al.* How to set up a database? a five-step process. *J Thorac Dis*. 2018 Oct;10(S29):S3533–8.

91. European Medicine Agency. Guideline for good clinical practice E6(R2) Step 5. 2016. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf

92. MSM Screening Study group, Jansen K, Steffen G, Potthoff A, Schuppe AK, Beer D, *et al.* STI in times of PrEP: high prevalence of chlamydia, gonorrhea, and mycoplasma at different anatomic sites in men who have sex with men in Germany. *BMC Infect Dis*. 2020 Dec;20(1):110.

93. Tongtoyai J, Todd CS, Chonwattana W, Pattanasin S, Chaikummao S, Varangrat A, *et al.* Prevalence and Correlates of Chlamydia trachomatis and Neisseria gonorrhoeae by Anatomic Site Among Urban Thai Men Who Have Sex With Men. *Sex Transm Dis*. 2015 Aug;42(8):440–9.

94. Dron L, Kalatharan V, Gupta A, Haggstrom J, Zariffa N, Morris AD, *et al*. Data capture and sharing in the COVID-19 pandemic: a cause for concern. *Lancet Digit Health.* 2022 Oct;4(10):e748–56.

95. Williams G.A. COVID-19 and the use of digital health tools: opportunity amid crisis that could transform health care delivery, 2022. Available from: https://apps.who.int/iris/bitstream/handle/10665/351081/Eurohealth-28-1-29-34-eng.pdf?sequence=1&isAllowed=y

96. Bittleston H, Goller JL, Temple-Smith M, Hocking JS, Coombe J. Telehealth for sexual and reproductive health issues: a qualitative study of experiences of accessing care during COVID-19. Gupta S, editor. *Sex Health*. 2022 Jun 23;19(5):473–8.

97. Mahtta D, Daher M, Lee MT, Sayani S, Shishehbor M, Virani SS. Promise and Perils of Telehealth in the Current Era. *Curr Cardiol Rep*. 2021 Sep;23(9):115.

98. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Republished research: Implementation research: what it is and how to do it: Implementation research is a growing but not well understood field of health research that can contribute to more effective public health and clinical policies and programmes. This article provides a broad definition of implementation research and outlines key principles for how to do it. *Br J Sports Med.* 2014 Apr;48(8):731–6.

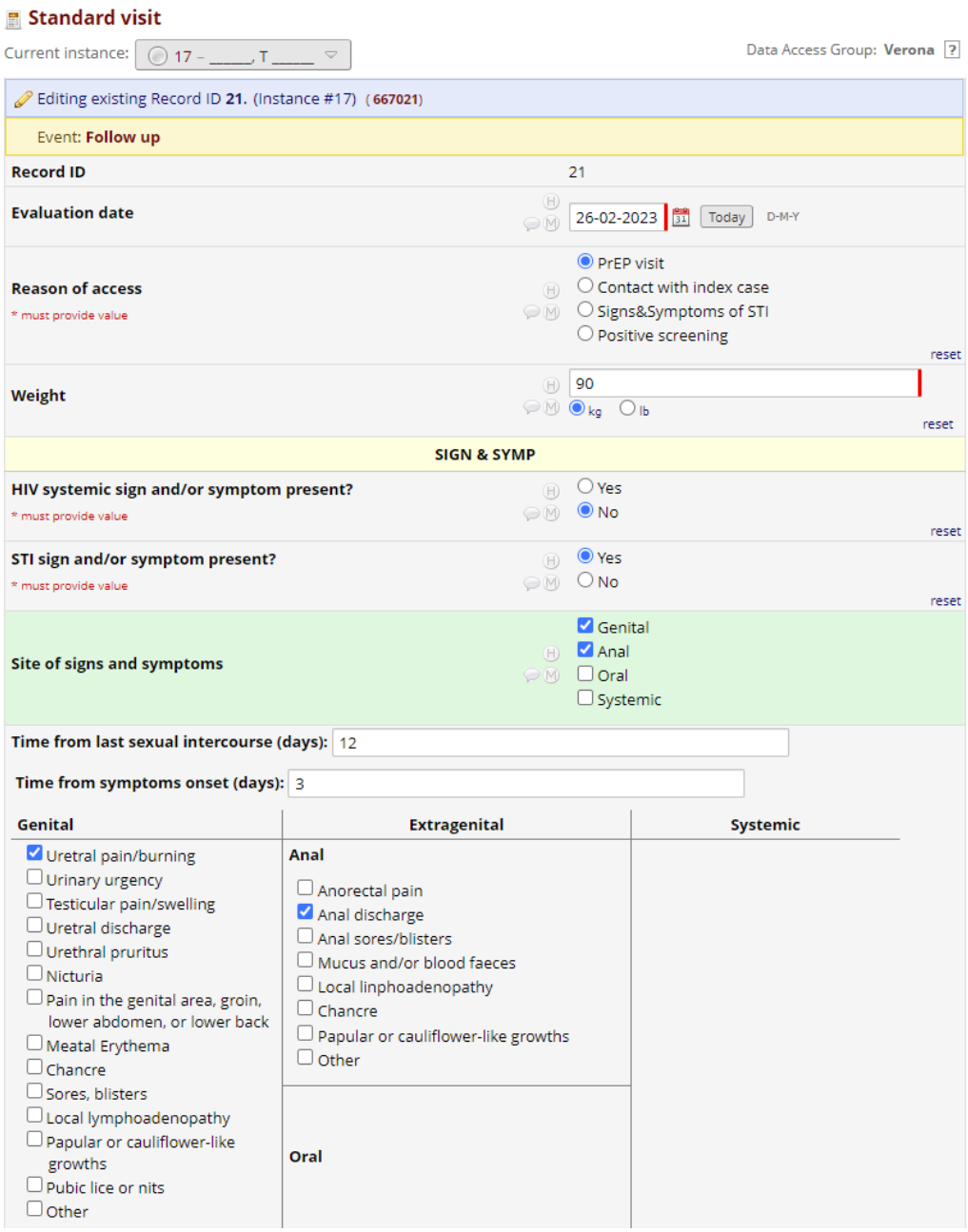
99. Peters D.H, Tran NT, Adam T. WHO. Implementation research in health. A practical guide. 2013. Available from: https://apps.who.int/iris/handle/10665/91758

100. Coyer L, van den Elshout MAM, Achterbergh RCA, Matser A, Schim van der Loeff MF, Davidovich U, *et al.* Understanding pre-exposure prophylaxis (PrEP) regimen use: Switching and discontinuing daily and event-driven PrEP among men who have sex with men. *EClinicalMedicine.* 2020 Dec;29–30:100650.

101. Hassoun-Kheir N, van Werkhoven CH, Dunning J, Jaenisch T, van Beek J, Bielicki J, *et al*. Perpetual observational studies: new strategies to support efficient implementation of observational studies and randomized trials in infectious diseases. *Clin Microbiol Infect*. 2022 Dec;28(12):1528–32.

ANNEX

Figure A1. Full content of the Standard Visit Instrument



Standard visit

Current instance: 17 – _____, T _____ Data Access Group: Verona

Editing existing Record ID 21. (Instance #17) (667021)

Event: Follow up

Record ID	21
Evaluation date	26-02-2023 Today D-M-Y
Reason of access * must provide value	PrEP visit; Contact with index case; Signs&Symptoms of STI; Positive screening — reset
Weight	90 kg lb — reset

SIGN & SYMP

HIV systemic sign and/or symptom present? * must provide value	Yes; No — reset
STI sign and/or symptom present? * must provide value	Yes; No — reset
Site of signs and symptoms	Genital; Anal; Oral; Systemic

Time from last sexual intercourse (days): 12

Time from symptoms onset (days): 3

Genital	Extragenital	Systemic
Uretral pain/burning	**Anal**	
Urinary urgency	Anorectal pain	
Testicular pain/swelling	Anal discharge	
Uretral discharge	Anal sores/blisters	
Urethral pruritus	Mucus and/or blood faeces	
Nicturia	Local linphoadenopathy	
Pain in the genital area, groin, lower abdomen, or lower back	Chancre	
Meatal Erythema	Papular or cauliflower-like growths	
Chancre	Other	
Sores, blisters		
Local lymphoadenopathy	**Oral**	
Papular or cauliflower-like growths		
Pubic lice or nits		
Other		

SEXUAL BEHAVIOUR LAST 3 MONTHS

Has sexual behavior been evaluated?
* must provide value
(H) (M) ◉ Yes ○ No
reset

Has the patient had sex? (include any type of sex: oral and/or vaginal or anal intercourses)
* must provide value
(H) (M) ◉ Yes ○ No
reset

Specify sexual behaviour
(H) (M) ◉ MSM ○ MSMW ○ MSW
reset

Steady partner(s)

Male SP(s)

Total	N° of know HIV+	N° of HIV in TASP
1	0	

Non steady partner(s)

Male NSP

Total	N° of know HIV+	N° of HIV in TASP
13	1	1

Oral intercourse

Has the patient had oral intercourse?
* must provide value
(H) (M) ◉ Yes ○ No
reset

COI with males

N° of partners the patient had COI with	% condomless OI
2	100

Anal intercourse

Has the patient had anal intercourse?
* must provide value
(H) (M) ◉ Yes ○ No
reset

Role
(H) (M) ○ Insertive ○ Receptive ◉ Both
reset

AI with SP

Total	CRAI	CIAI
13	4	4
	Date: 17-02-2023 Today D-M-Y	Date: 17-02-2023 Today D-M-Y

AI with NSP

Total	CRAI	CIAI
20	6	6
	Date: 18-02-2023 Today D-M-Y	Date: 18-02-2023 Today D-M-Y

AI with HIV+ partner(s)

Total	CRAI	CIAI
3	1	1
	Date: 19-02-2023 Today D-M-Y	Date: 19-02-2023 Today D-M-Y

Group sex

Have the patient had group sex?	(•) Yes ( ) No reset
How often? (how many times/3 months)	4

STIs CONTACT

Contact with STI index case?	(•) Yes ( ) No reset
Type of STI contact	[ ] Syphilis [x] Gonorrea [ ] Mycoplasma genitalium [ ] Chlamydia [ ] HIV [ ] HBV [ ] HCV [ ] HAV [ ] Monkeypok

CHEMSEX

Chemsex drugs use	(•) Yes ( ) No reset
Which recreational substance(s) does the patient use (specify n° of times in the last 3 months)	[ ] alcohol [ ] hashish [ ] popper/ethilcloride [ ] cocaine intravenous [ ] cocaine smoked [ ] cocaine sniff [ ] cocaine intramuscolar [ ] amphetamines [ ] MDMA/ecstasy [ ] mephedrone intravenous [ ] mephedrone intramuscolar [ ] mephedrone sniff [x] mepherone smoked 3 [ ] mephedrone enema

	☐ GHB/GLB ☐ methamphetamine intravenous ☐ methamphetamine intramuscolar ☐ methamphetamine sniffed ☐ methamphetamine eaten ☐ methamphetamine smoked ☑ viagra/cialis 1 ☐ αPHP ☐ Ketamine endovenous ☐ Ketamine intramuscolar
PrEP	
Patient on PrEP?	◉ Yes ○ No reset

Ongoing PrEP regimen	N° forgotten pills	% pills forgotten
◉ daily ○ on-demand reset	3	98

TDF/FTC adverse events	☐ none ☑ headache ☐ dizziness ☐ insomnia ☐ nightmares ☐ nausea ☐ diarrhea ☐ abdominal pain ☐ skin rash ☐ itch ☐ myalgia ☐ fatigue ☐ pain ☐ other
PrEP prescribed? (if yes specify regimen type)	◉ Yes ◉ daily ○ on-demand reset ○ No reset
MICROBIOLOGY	
Have microbiology specimens been collected?	◉ Yes ○ No reset
Which samples were collected?	☑ Pharyngeal swab ☐ Urine ☑ Urethral swab ☐ Rectal swab ☑ Skin lesion swab ☐ Other
PHARYNGEAL SAMPLE	
NAAT results	☐ Negative ☑ Neisseria gonorrhoeae ☐ Mycoplasma genitalium ☐ Chlamydia trachomatis ☐ Other

N. gonorrhoeae

New infection? ◉ Yes ○ No

reset

TOC performed?	New antibiotic prescribed? (if yes specify prescription date)	TOC result	Possible reasons for TF
○ Yes ○ No reset		**Date:**	

URETHRAL SAMPLE

Results	☐ Negative ☑ Neisseria gonorrhoeae ☐ Mycoplasma genitalium ☐ Chlamydia trachomatis ☐ Other

N. gonorrhoeae

New infection? ○ Yes ○ No

reset

TOC performed?	New antibiotic prescribed? (if yes specify prescription date)	TOC result	Possible reasons for TF
◉ Yes ○ No reset	○ Yes ○ No reset	**Date:** 01-03-2023 Today D-M-Y ◉ Positive ○ Negative reset	☐ Medications not taken correctly ☐ Re-exposure to untreated partener ☑ Infection acquired from a new partner ☐ False positive result ☐ Resistence

SEROLOGIES

Serology requested	☐ None ☑ HIV ☐ HAV ☐ HBV ☐ HCV ☑ Syphilis

HIV

	Result	New infection?
Ab	○ Pos ◉ Neg reset	
Ag	○ Pos ◉ Neg reset	
RNA		

SIPHYLIS

Tests

- [ ] Rapid plasma reagin (RPR)
- [x] VDRL
  - (•) Reactive
  - ( ) Non reactive

reset

- [ ] Complement fixation/Wasserman reaction
- [x] Chemiluminescence immunoassay (CLIA)
  - (•) Reactive
  - ( ) Non reactive

reset

- [ ] T. pallidum enzyme immunoassay (TP-EIA)
- [ ] Fluorescent treponemal antibody absorption (FTA-ABS)
- [ ] T.pallidum immobilization assay (TPI)
- [x] T.pallidum passive particle agglutination assay (TPPA)
  - (•) Reactive
  - ( ) Non reactive

reset

- [ ] Microhemagglutination assay for T.pallidum (MHA-TP)

VDRL titer	
=	64

TPPA titer	
>	20560

SYPHILIS INFECTION

Siph new infection

- (•) Yes
- ( ) No

reset

Siphilis infection stage

- ( ) Primary
- ( ) Secondary
- (•) Early latent
- ( ) Late latent
- ( ) Tertiary
- ( ) Neurosiphylis

reset

ANTIMICROBIAL THERAPY

Antimicrobial therapy prescribed?

- (•) Yes
- ( ) No

reset

ROUTINE EXAMS

Routine exams

- [x] None
- [ ] Urine
- [ ] Serum