Sustained Reduction of Bacterial STIs During the DoxyPEP Study Open-Label Extension

Abstract Submission Number:

125

Abstract Type:

General Abstract Submission

Authors:

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Background:

After early demonstration of 65% efficacy in reducing bacterial STIs in the DoxyPEP Study, participants (ppts) in the standard of care (SOC) arm were offered doxy-PEP. We subsequently examined uptake, adherence, sexual activity, and incident bacterial STIs, as awareness of STI prevention efficacy may impact patterns of doxy-PEP use and sexual behavior.

Methods:

DoxyPEP is an open-label trial conducted in Seattle and San Francisco among men who have sex with men (MSM) and transwomen (TW) living with HIV (PWH) or on PrEP who had a bacterial STI in the past year, randomized 2:1 to doxy-PEP or SOC. After the efficacy threshold was reached in a planned interim analysis, SOC ppts were offered

doxy-PEP and both arms were followed in an open label extension (OLE) for up to 12 months total. OLE quarters were defined as those with doxy-PEP for a full quarter after 5/2022 results were disclosed. Self-reported sexual behavior and quarters with ≥1 STI endpoint are compared descriptively during OLE doxy-PEP use vs. SOC as-randomized (SOC-AR) without doxy-PEP.

Results:

Of the 637 ppts enrolled, 279 contributed to OLE follow-up: 193 from the doxy-PEP arm (D-OLE) and 86 of 87 ppts from the SOC arm (SOC-OLE). Of those in the OLE: 96% MSM, 4% TW, 78% were on PrEP, 22% PWH, 62% White, 4% Black, 13% Asian, 22% other; 27% Hispanic. ≥1 STI endpoints were observed in 13.4% of D-OLE and 18.2% of SOC-OLE quarters, compared to 12.1% during doxy-PEP as-randomized (D-AR) and 31.2% during SOC-AR (Table). Reductions in each STI (gonorrhea, chlamydia and syphilis) were observed in both D-OLE and SOC-OLE groups compared to the SOC-AR. Doxy-PEP use after condomless sex was 78% in D-OLE and 79% in SOC-OLE ppts, compared to 83% of D-AR ppts. Median self-reported doxy doses taken per quarter were 19 (IQR 7-32) in D-OLE and 16 (5-30) in SOC-OLE, compared to 14 (IQR 4-30) during D-AR. During OLE, SOC-OLE ppts reported higher median sex partners per quarter: 15 (IQR 5-30) compared to 8 (IQR 4-15) during SOC-AR and D-OLE ppts reported a median of 12 (IQR 5-25) partners per quarter vs.10 (IQR 4-25) during D-AR.

Conclusions:

In the OLE period after doxy-PEP efficacy was known, almost all SOC ppts accepted doxy-PEP and both OLE groups reported high doxy-PEP coverage (>78%) of condomless sex in the context of a higher number of sexual partners during OLE. Doxy-PEP was associated with sustained decreased rates of incident STI's in both groups during the OLE compared to no doxy-PEP use among ppts initially randomized to the SOC arm.

Epidemiology/Public Health:

(T) Contraception, Sexually Transmitted Infections, and Reproductive Health in Adults

Search Terms:

Doxycycline
Men who have sex with men
Postexposure prophylaxis
Sexually transmitted infection

Table: STI endpoints, sex partners, and doxycycline PEP use among DoxyPEP study participants in the 'as-randomized' (2:1 to doxy-PEP and standard of care, SOC) period and 'open label extension' (OLE, after efficacy results were released May 2022)

	As-randomized (AR)		Open Label Extension (OLE)	
	Doxy-PEP n quarters = 1078	Standard of care (SOC) n quarters = 462	Doxy OLE (doxy-PEP → doxy-PEP) n quarters = 397	SOC OLE (SOC → doxy-PEP) n quarters = 165
Quarters with ≥ 1 STI endpoint (%, 95% CI)	12.1% (10.1%–14.0%) n = 130	31.2% (26.9%–35.4%) n = 144	13.4% (10.0%–16.7%) n = 53	18.2% (12.3%–24.1%) n = 30
Quarters with gonorrhea (%, 95% CI)	9.4% (7.6%–11.1%) n = 101	19.3% (15.7%–22.9%) n = 89	10.3% (7.3%–13.3%) n = 41	12.7% (7.6%–17.8%) n = 21
Quarters with chlamydia (%, 95% CI)	2.6% (1.6%–3.5%) n = 28	12.8% (9.7%–15.8%) n = 59	1.8% (0.5%–3.1%) n = 7	4.2% (1.2%–7.3%) n = 7
Quarters with syphilis (%, 95% CI)	0.6% (0.2%–1.1%) n = 7	3.2% (1.6%–4.9%) n=15	1.3% (0.2%–2.4%) n = 5	1.2% (-0.5%–2.9%) n = 2
Sex partners per quarter (median, IQR)	10 (4–25)	8 (4–15)	12 (5–25)	15 (5–30)
Doxy doses per quarter (median, IQR)	14 (4–30)	N/A	19 (7–32)	16 (5–30)
% of condomless sex acts covered by doxy-PEP per quarter	83.1%	N/A	78.0%	79.0%

Doxycycline PEP: High Uptake and Significant Decline in STIs After Clinical Implementation

Abstract Submission Number:

126

Abstract Type:

General Abstract Submission

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Presenting Author:

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Background:

Doxycycline as bacterial sexually transmitted (STI) post-exposure prophylaxis (DPEP) has shown high prevention efficacy in clinical trials. We evaluated the uptake and impact of DPEP on Chlamydia (CT), Gonorrhea (GC), and Syphilis incidence among PrEP users in a sexual health clinic in San Francisco.

Methods:

DPEP was offered to all active PrEP clients at their clinical visits starting on 11/30/22. We included PrEP clients with at least one STI test who received DPEP for at least 30 days (DPEP users), or never initiated DPEP (non-DPEP users). The "pre-DPEP" period was defined as 6/1/22-11/30/22; and the "post-DPEP" period started after DPEP initiation for DPEP users. STI testing included GC and CT (urine, rectal, and pharyngeal), and syphilis. Adjusted STI incidence rate ratios (IRR) per quarter for the pre- and post-DPEP periods were evaluated, and a controlled interrupted time series

(CITS) analysis with mixed-effects Poisson regression used to evaluate intervention effects.

Results:

Of the 3,081 active PrEP clients, 1,209 (39%) received DPEP during the study period. Those who received DPEP were racially/ethnically diverse with 33% White, 26% Latinx, 16% Asian, and 4% Black; and the majority were cisgender men (90%), gay (91%), and 30-49 years (62%). The demographics of non-DPEP users were similar to DPEP users. Among DPEP users, any STI incidence declined from 18.1% in the first quarter of the study period to 7.5% in the last quarter. Among non-DPEP users, any STI incidence was stable between the first and last quarter: 7.0% and 6.5%, respectively. In the pre-post-DPEP analysis, DPEP was associated with decreased STI incidence for any STI [IRR: 0.42, 95% Confidence Interval (95% CI): 0.24-0.74; p=0.003], CT (IRR: 0.33, 95% CI: 0.23-0.46; p<0.001), and syphilis (IRR: 0.22, 95% CI: 0.07-0.54; p=0.001); but not GC (IRR: 0.89, 95% CI: 0.69-1.15; p=0.383). In the CITS analysis DPEP was associated with a significant decline in the slope for any STI incidence among PrEP clients (IRR: 0.67, 95% CI: 0.46-0.96; p=0.03) (Figure 1). This decline was also significant for CT (p=0.021) and GC (p=0.003), but not syphilis (p=0.360).

Conclusions:

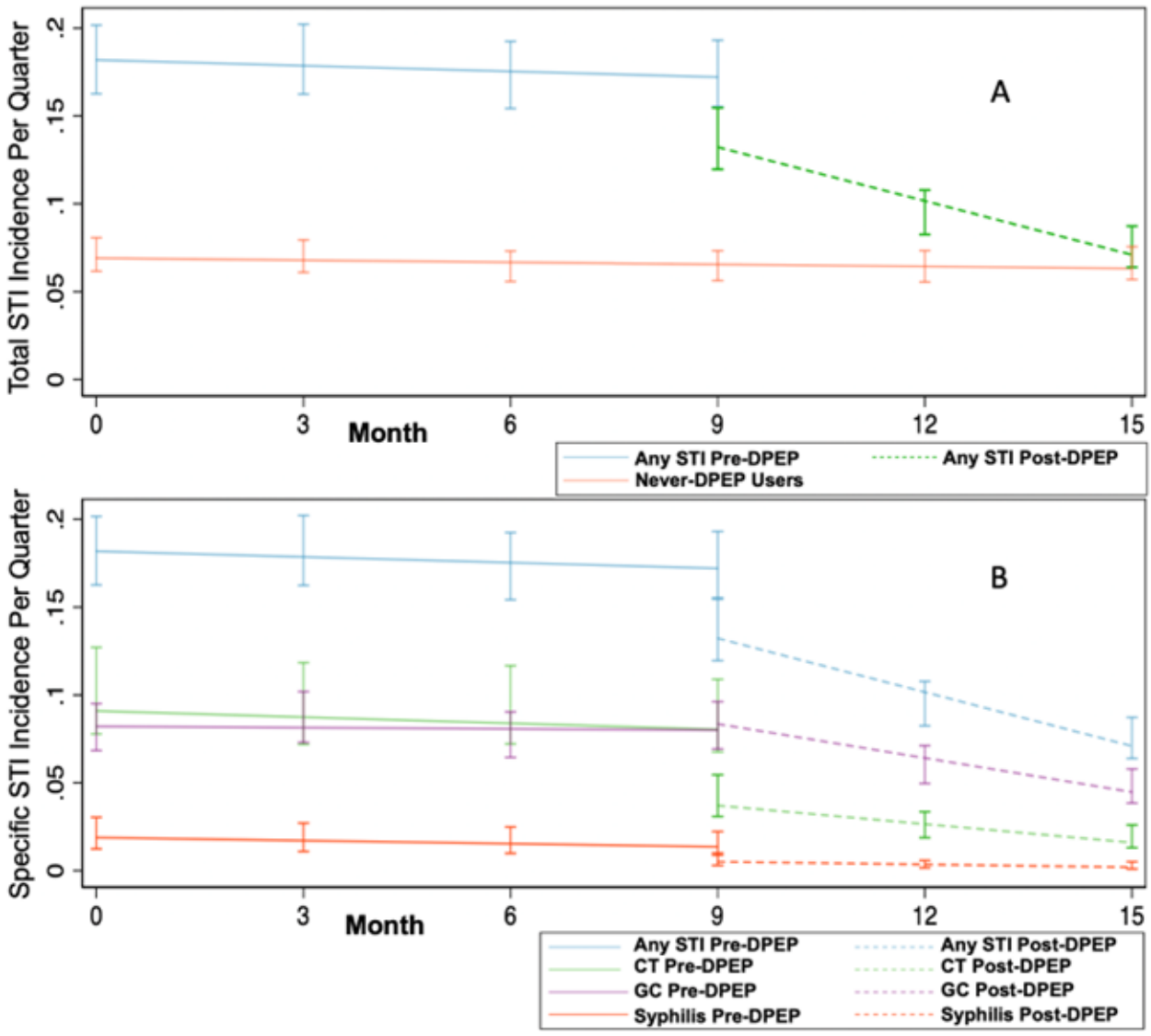
DPEP uptake was high reflecting strong demand when offered as part of routine PrEP care. Overall STI incidence declined rapidly after implementation demonstrating high impact of this intervention in a real-world setting. Continued evaluation of uptake, adherence, and impact on bacterial STIs will be essential as DPEP implementation expands.

Epidemiology/Public Health:

(T) Contraception, Sexually Transmitted Infections, and Reproductive Health in Adults

Search Terms:

Sexually transmitted infection


Total STI Incidence Per Quarter
0
.05
.1
.15
.2
A
0
3
6
9
12
15
Month
Any STI Pre-DPEP
Never-DPEP Users
Any STI Post-DPEP
Specific STI Incidence Per Quarter
0
.05
.1
.15
.2
B
0
3
6
9
12
15
Month
Any STI Pre-DPEP
CT Pre-DPEP
GC Pre-DPEP
Syphilis Pre-DPEP
Any STI Post-DPEP
CT Post-DPEP
GC Post-DPEP
Syphilis Post-DPEP

Doxy-PEP Associated With Declines in Chlamydia and Syphilis in MSM and Trans Women in San Francisco

Abstract Submission Number:

127

Abstract Type:

Late Breaking Abstract

Authors:

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Background:

In October 2022, the San Francisco (SF) Department of Public Health disseminated guidelines through community and public health networks recommending doxycycline post-exposure prophylaxis (doxy-PEP) for men who have sex with men (MSM) and transgender women (TGW) with a history of sexually transmitted infections (STIs) or multiple sex partners. Doxy-PEP's effect on population-level incidence of STIs is unknown.

Methods:

To monitor doxy-PEP uptake at sentinel sites, we tracked the quarterly number of new patients initiating doxy-PEP from three high-volume SF sexual health clinics. To assess the ecological association between doxy-PEP program implementation and citywide STI

incidence, we conducted interrupted time series analyses on monthly reported SF cases of chlamydia (CT), gonorrhea (GC), and early syphilis (ES), among MSM/TGW before (7/1/21–10/31/22) and after (11/1/22–11/30/23) release of doxy-PEP guidance, and used autoregressive integrated moving average (ARIMA) models to forecast expected post-period monthly case counts in the absence of doxy-PEP. Observed case counts were based on citywide surveillance data. Analyses were repeated for monthly CT case counts among cis women for comparison.

Results:

From 11/1/22 to 9/30/23, 3,288 MSM/TGW initiated doxy-PEP at the three sentinel clinics. Citywide, the number of monthly reported CT (-6.7%/month, $p<0.0001$) and ES (-3.12%/month, $p<0.0001$) cases among MSM/TGW decreased significantly after the release of doxy-PEP guidelines compared to model forecasts (Figure). By the end of the 13-month post-period, CT and ES cases decreased 51% (95% CI: 39%-60%) and 50% (95% CI: 38%-59%), respectively, compared to expected counts in November 2023. No significant change in GC cases was seen ($p=0.087$). Among cis women, the number of monthly reported CT cases in the post-period increased significantly (2.43%/month, $p<0.01$).

Conclusions:

Release of SF doxy-PEP guidelines and early implementation at high volume clinics were associated with a substantial sustained decrease in reported SF cases of CT and ES, but not GC, among MSM/TGW over a 13-month period. Other factors, including changes in screening and sexual practices (e.g., in response to mpox), may have contributed to observed trends. Future analyses are planned with extended post-period data to determine whether observed trends continue to align with citywide doxy-PEP uptake and to assess for demographic disparities in doxy-PEP uptake and STI incidence.

Epidemiology/Public Health:

(T) Contraception, Sexually Transmitted Infections, and Reproductive Health in Adults

Search Terms:

DoxyPEP
MSM
Sexually transmitted infection
STD surveillance
Transgender women

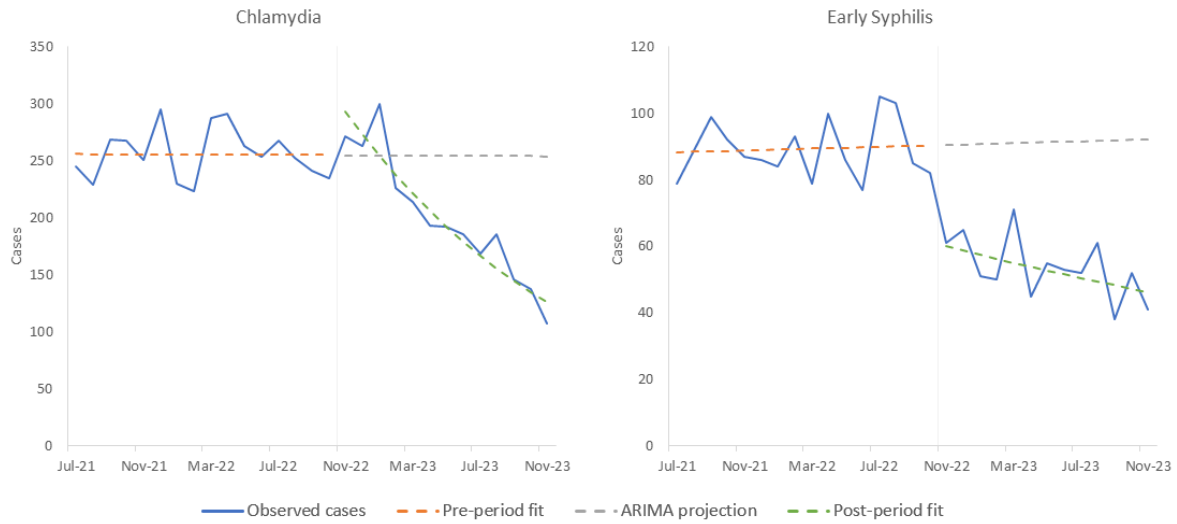

Figure. Observed and modelled chlamydia and early syphilis cases among MSM and TGW in San Francisco pre and post doxy-PEP implementation

Safety Profile and Immunogenicity of a Phase I Clinical Trial Using Germline-Targeting Trimer GT1.1

Abstract Submission Number:

100

Abstract Type:

General Abstract Submission

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Background:

An effective HIV-vaccine should induce broadly neutralizing antibodies (bNAbs) targeting the viral envelope glycoprotein, which is challenged by the low frequencies of bNab precursor B cells. Pre-clinical studies have shown the ability of the BG505 SOSIP.GT1.1 gp140 (GT1.1) vaccine to prime bNAb precursor B cells, including those targeting the CD4-binding site. Here, we report the first safety and immunogenicity data from a first in-human clinical trial using GT1.1.

Methods:

This phase I, double-blinded, placebo-controlled, dose-escalating vaccination trial was conducted at two US sites and one in the Netherlands. Participants received intramuscular injections of either 30µg (low-dose) or 300µg (high-dose) of the GT1.1 vaccine with AS01B adjuvant system, or saline placebo at 0, 8, and 24 weeks. Reactogenicities were reported during the 15 days post-vaccinations, Serious AEs for

the entire study period. Serum antibody binding and neutralization responses were quantified using BAMA and TZM-bl pseudovirus neutralization assays, respectively.

Results:

We enrolled 47 adults without HIV (low-dose: n=20, high-dose: n=19, placebo: n=8), with an average age of 30 years and an similar sex distribution between groups. Ninety-four percent of participants reported at least one solicited Adverse Event (AE). Most AEs were graded mild (59.2%) or moderate (37.7%). There were no significant differences in number of AEs between the vaccine administrations (Chi-Squared test, p=0.17), or dose groups (p=0.13). No vaccine-related Serious AEs were reported. All vaccinated participants developed detectable GT1.1-binding serum antibodies at weeks 10 and 26, with the high-dose recipients showing a higher response rate after the first vaccination (10.5% low- vs. 31.5% high-dose) and significantly higher responses at week 10 (p=0.008) (Fig. 1A). GT1.1 neutralizing antibodies (NAb) were more prevalent in the high- compared to the low-dose recipients after the second (68% vs. 28%, respectively) and third vaccination (100% vs. 89%, respectively)(Fig.1B). Serum NAb activity was at least in part directed against the CD4-binding site

Conclusions:

The adjuvanted GT1.1 vaccine has an acceptable safety and reactogenicity profile and induced a potent vaccine-specific serum antibody response. Here, a higher GT1.1 dose induced a more rapid and robust serum antibody binding response without compromising safety. Thus, germline-targeting trimer GT1.1 may represent a promising vaccine candidate for priming bNAb responses in humans.

Basic Science:

(C) Host Immune Responses, Vaccines, and Immunotherapies: HIV, SARS-CoV-2, or Mpox Virus

Search Terms:

Adverse event
Antibody response
HIV vaccine
Neutralization
Phase I

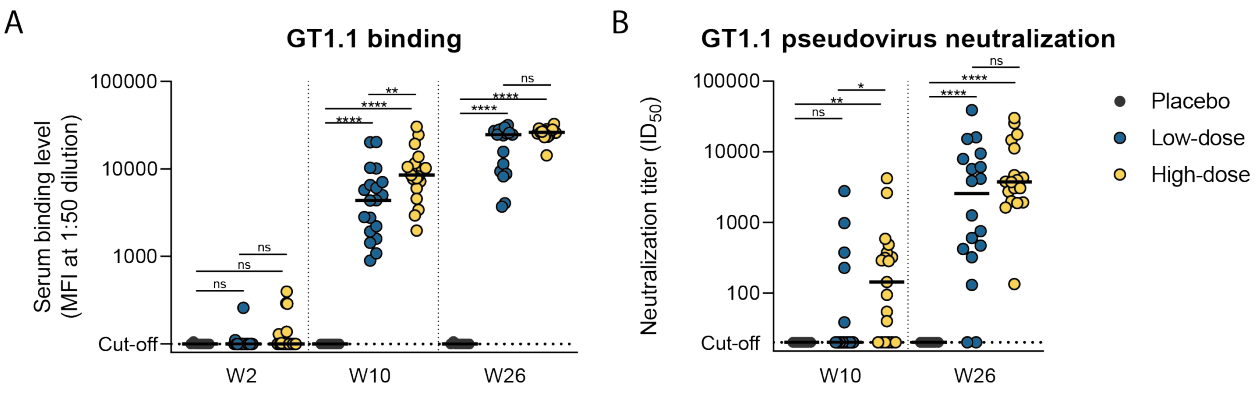

Figure 1. Serum antibody responses against BG505 SOSIP.GT1.1 gp140 following GT1.1 vaccination. Serum IgG binding (A) and neutralization responses (B). MFI: Median Fluorescent Intensity, ID_{50}: 50% inhibitory dilution. Serum responses were compared using a Mann-Whitney U test. P>0.05: ns, p<0.05:* p<0.01:**, p<0.0001: ****

CD4 Binding Site Glycan-Deficient SHIVs Elicit Broadly Neutralizing Antibodies in Rhesus Macaques

Abstract Submission Number:

103

Abstract Type:

General Abstract Submission

Authors:

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Background:

Previous work has demonstrated that modifying soluble HIV-1 envelope (Env) trimers to remove glycans around the CD4 binding site (CD4bs) can immunofocus potent neutralizing antibody (NAb) responses to this epitope. However, such immunogens generally did not elicit broadly neutralizing antibodies (bNAbs). Understanding how to better boost these responses can inform vaccine design. Infection of rhesus macaques with replicating simian-human immunodeficiency viruses (SHIVs) bearing WT glycan-intact Envs rarely elicits bNAbs targeting the CD4bs. Here, we designed novel SHIVs lacking glycans surrounding the CD4bs (197, 363, and 462) to test the hypothesis that infection with these evolving SHIVs could immunofocus, boost, and affinity-mature CD4bs-targeted NAb and bNAb responses.

Methods:

We disrupted glycosylation sequons at the above residues in three SHIVs bearing primary transmitted/founder Envs (CH505, BG505 and CH1012) and used these to intravenously infect a pilot cohort of 14 rhesus macaques (RMs). RMs were monitored to evaluate viral kinetics, Env sequence evolution, and NAb and bNAb development.

Results:

9 of 14 RMs exhibited ideal viral kinetics for further analysis. All 9 RMs developed potent autologous neutralizing responses targeting the protein surface beneath the engineered glycan hole. 4 of 9 RMs developed responses capable of neutralizing heterologous glycan-deficient viral strains. Longitudinal sequencing of plasma viral RNA revealed rapid, sequential restoration of the deleted glycans as well as CD4bs bNAb escape mutations arose temporally with rising neutralizing titers. Two RMs developed antibody responses capable of neutralizing WT heterologous viruses. Based on these results, we downselected from these constructs SHIV.CH505.CD4bs.GH to infect an additional 8 RMs. We observed CD4bs-targeted neutralization breadth in an additional 6 RMs. Epitope mapping of these broad responses showed that 7 of 8 RMs targeted the CD4bs.

Conclusions:

These results show that SHIV Env trimers with targeted glycan deletions can immunofocus B cell responses to the CD4bs. Viral evolution in response to these glycan hole targeted NAbs can boost and affinity mature these responses, in some cases leading to bNAbs that target WT heterologous viruses with intact glycan shields. Ongoing studies will isolate and characterize mAbs responsible for this breadth and analyze Env-Ab coevolution to identify key Envs that can be selected as priming and boosting immunogens.

Basic Science:

(C) Host Immune Responses, Vaccines, and Immunotherapies: HIV, SARS-CoV-2, or Mpox Virus

Search Terms:

broadly neutralizing antibodies
CD4-binding site
Glycan
Rhesus macaques
SHIV

Therapeutic Efficacy of a Triple Combination of HIV-1 Broadly Neutralizing Antibodies

Abstract Submission Number:

121

Abstract Type:

Late Breaking Abstract

Authors:

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Background:

Human immunodeficiency virus type 1 (HIV-1) specific broadly neutralizing monoclonal antibodies (bNAbs) have to date shown limited therapeutic efficacy when administered as monotherapy or as a cocktail of two antibodies. A combination of three bNAbs provides improved neutralization coverage of global viruses. Here we show that a triple bNAb cocktail targeting three distinct epitopes on HIV-1 Env results in long-term virologic control in persons living with HIV-1 (PLWH) following discontinuation of antiretroviral therapy (ART).

Methods:

We first evaluated the pharmacokinetics of the bNAbs PGT121, PGDM1400, and VRC07-523LS, which target the V3 glycan supersite, V2 apex, and CD4 binding site, respectively. We then assessed the therapeutic efficacy of up to six monthly infusions of this triple bNAb cocktail in 12 PLWH who discontinued ART after the first antibody infusion (NCT03721510). Participants were not screened for bNAb sensitivity at baseline.

Results:

83% of participants (10 of 12) maintained virologic suppression for the duration of the antibody dosing period for at least 28 weeks. Moreover, 42% of participants (5 of 12) demonstrated virologic suppression for the duration of follow-up for at least 38-44 weeks, despite the decline of serum bNAb concentrations to low or undetectable levels. Early viral rebound in 2 individuals correlated with baseline resistance to PGT121 and PGDM1400, whereas late viral rebound in 5 participants in the context of declining bNAb levels was characterized by both sensitive and resistant rebound virus.

Conclusions:

Our data demonstrate the potential of a triple HIV-1 bNAb cocktail to provide long-term virologic control in the majority of PLWH in the absence of ART. Long-acting versions of these three bNAbs are currently being developed for HIV-1 prevention and therapy.

Clinical:

(G) Antiviral Therapy: Pre-Clinical Data, Randomized Trials, Efficacy, and Effectiveness Studies in HIV or SARS-CoV-2 or Mpox Virus in Adults

Search Terms:

ART disruption
bNAb
bNAb resistance
Viral control

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Randomized Trial of Cabotegravir and Rilpivirine Long-Acting in Africa (CARES): Week 48 Results

Abstract Submission Number:

122

Abstract Type:

Late Breaking Abstract

Authors:

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Institutions:

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Presenting Author:

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Background:

Long-acting injectable therapy (LA) is a recommended option for individualized treatment of human immunodeficiency virus type 1 (HIV-1) infection in resource-rich settings. Additional evidence is required to determine the role of LA for treatment programs in Africa, where demographic factors, viral subtypes, prior treatment exposure, prevalence of pre-existing antiviral drug resistance and standardized approach to treatment delivery and monitoring differ.

Methods:

This ongoing phase 3b randomized, multicentre, open-label trial evaluates efficacy, safety, and tolerability of switching from oral antiretroviral therapy (ART) to LA. HIV-1

positive adults, stable on first-line ART (TDF +3TC/FTC+EFV/NVP/DTG) with VL <50 copies/ml at screening were enrolled at 8 African sites. Main exclusion criteria were past virologic failure, pregnancy and HBV infection. Participants were randomized (1:1) to continue oral ART (OT group) or switch to cabotegravir (CAB) and rilpivirine (RPV) intramuscular injections every 8 weeks (LA group). VL was monitored every 24 weeks. Primary outcome was the proportion of participants with VL <50 copies/ml at week 48, by FDA snapshot algorithm (non-inferiority margin 10%). Confirmed virologic failure (CVF, secondary outcome) was defined as 2 consecutive VL ≥200 copies/ml. Resistance testing was done retrospectively on archived DNA at baseline in all participants, and at CVF.

Results:

512 participants were enrolled (median age 42y; 58% female; 92% on DTG-based ART; 74% with prior NNRTI exposure; 14% baseline archived RPV resistance mutations; 57% viral subtype A1; 21% baseline BMI ≥30kg/m2). Four withdrew by week 48 (2 LA, 2 OT group). At 48 weeks, 248/255 (97.3%) in LA and 252/257 (98.1%) in OT group had VL<50 copies/mL (difference -0.8%; 95%CI -3.4 to 1.8%); demonstrating non-inferiority (Table). One participant in LA group met the definition of CVF. Adverse events of grade ≥3 severity occurred in 24 (9%) in LA and 10 (4%) in OT group; only one adverse event in LA led to treatment discontinuation (injection-site abscess).Treatment satisfaction increased after switching to long-acting therapy.

Conclusions:

At 48 weeks, CAB and RPV LA showed non-inferior efficacy to standard oral ART when used in the public health approach with sparse VL monitoring and where pre-existing RPV resistance, subtype A1 virus and obesity are common. CVF and acquired resistance was rare. LA was effective and safe and may be considered for use in treatment programs in sub-Saharan Africa.

Clinical:

(G) Antiviral Therapy: Pre-Clinical Data, Randomized Trials, Efficacy, and Effectiveness Studies in HIV or SARS-CoV-2 or Mpox Virus in Adults

Search Terms:

Antiviral Therapy for HIV
Long Acting Drugs
Africa
Randomized trial

Outcome	LA group (n=255)	OT group (n=257)	Difference (95% CI)
HIV-1 RNA level (primary outcome, ITT, adjusted) – no (%)			
< 50 copies/ml	248 (97.3)	252 (98.1)	-0.8 (-3.4 to 1.8)
≥ 50 copies/ml	5 (2.0)	3 (1.2)	0.8 (-1.8 to 3.4)
No virological data	2 (0.8)	2 (0.8)	-
Main secondary outcome			
Confirmed virological failure (≥ 200 copies/ml, ITT) – no (%) *	1 (0.4)	0	0.4 (-0.3 to 1.2)

Table: main virological outcomes by randomised group

* Mutations to rilpivirine (V108I, E138K and V179L) and cabotegravir (E92E/V, N155H and L74M) at failure. One additional LA participant had VL≥ 200 copies/ml at week 48 that could not be confirmed (participant died before repeat); mutations to rilpivirine and cabotegravir were present.

MRNA Vaccine Versus Hybrid Immunity Against COVID-19 Among People With HIV During Omicron Wave

Abstract Submission Number:

133

Abstract Type:

General Abstract Submission

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Background:

CoVPN 3008 (Ubuntu), the largest multicenter phase 3/4 trial of mRNA vaccines in sub-Saharan Africa, was designed to assess the safety of mRNA-1273, the effectiveness of hybrid versus vaccine immunity, and SARS-CoV-2 viral persistence among people with HIV (PWH).

Methods:

We enrolled adults aged ≥18 years living with HIV or another comorbidity associated with severe Covid-19. Previously vaccinated individuals were excluded. Participants were assigned vaccinations at enrollment only or enrollment and month 1 based on whether their baseline point-of-care SARS-CoV-2 serostatus was positive (hybrid immunity) or negative (vaccine immunity). For the first 6 months of follow-up, the association between hybrid versus vaccine immunity with Covid-19 and severe Covid-19 was assessed using calendar-time-scale Cox regression models and counterfactual cumulative incidence methods.

Results:

Between December 2021 and September 2022, 14237 participants were enrolled, of which 11681 PWH (median age 39 years, 77% female) were included in the Full Analysis Subset (FAS). Among PLWH, the median CD4 count was 635 cells/mm^3 (IQR 423-866), 769 (6.6%) had a CD4 count <200 cells/mm^3, 2157 (18.5%) had a detectable viral load (≥50 copies/ml), and 14.5% were not on ART. Retention was high (>95%) through the month 6 visit. The vaccinations were well tolerated. Among PWH, the 6-month cumulative incidence (Fig1A) in the vaccine immunity and hybrid immunity groups, respectively, was 7.77% (95% confidence interval [CI] 6.21 to 9.23) and 3.90% (95% CI 3.30 to 4.49) for SARS-CoV-2 infection, 3.40% (95% CI 2.30 to 4.49) and 2.02% (95% CI 1.61 to 2.44) for Covid-19, and 0.32% (95% CI 0.59 to 0.63) and 0.048% (95% CI 0 to 0.1) for severe Covid-19. The covariate-adjusted hazard rate was 42% lower in the hybrid immunity group for Covid-19 (hazard ratio [HR] 0.58; 95% CI 0.44 to 0.77; p=<.001), and 73% lower (HR 0.27; 95% CI 0.07 to 1.04; p=0.056) in the hybrid immunity group for severe Covid-19 (Fig1B). Twenty-two individuals had persistent SARS-CoV-2 infection ≥50 days, which was more often among those with prior TB infection, HIV viremia, or low CD4 count.

Conclusions:

Individuals with hybrid immunity, even if living with HIV, were more effectively protected from Covid-19 and severe Covid-19 compared to those with vaccine immunity. Our results also highlight the importance of better understanding the role of persistent infections in transmission and in the emergence of new variants of concern through mutation evolution.

Epidemiology/Public Health:

(S) Prevention of HIV, COVID-19, and Mpox in Adults

Search Terms:

SARS CoV2
COVID-19
HIV
Hybrid immunity
Vaccines

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SARS-CoV-2 Viral Clearance and Evolution Varies by Extent of Immunodeficiency

Abstract Submission Number:

134

Abstract Type:

General Abstract Submission

Authors:

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Background:

Despite vaccination and antiviral therapies, immunocompromised individuals are at risk for prolonged SARS-CoV-2 infection, but the immune defects that predispose to persistent COVID-19 remain incompletely understood.

Methods:

Participants enrolled in the POSt-VaccInaTIon Viral CharactEristics Study (POSITIVES), a prospective cohort study enrolling participants with confirmed SARS-CoV-2 infection. Participants were categorized based on the extent of immunocompromise into severe hematologic malignancy/transplant group (S-HT), severe autoimmune/B-cell deficient (S-A), non-severe immunodeficiency (NS), and non-immunocompromised (None). Longitudinal nasal SARS-CoV-2 levels were measured with a quantitative PCR assay and viable virus levels were evaluated by viral culture. Neutralizing antibody, binding

antibody to nucleocapsid, and T cell profiling (enzyme-linked immunosorbent spot [ELISpot] and Spike-specific proliferation assay) were performed in a subset of participants with available blood samples.

Results:

The median time to nasal viral RNA and culture clearance in the severe hematologic malignancy/transplant group (S-HT) were 72 and 40 days, respectively, which were significantly longer than clearance rates in the severe autoimmune/B-cell deficient (S-A), non-severe, and non-immunocompromised groups (P=0.002 Figure 1A and P<0.001 Figure 1B). Individuals with B-cell deficiency (S-A group) had an intermediate risk of persistent infection. Participants who were severely immunocompromised (S-HT and S-A) had greater SARS-CoV-2 evolution and a higher risk of developing antiviral treatment resistance. Both S-HT and S-A participants had severely diminished SARS-CoV-2-specific humoral responses. In contrast, S-A group had the highest level of SARS-CoV-2-specific CD4+ and CD8+ T cell proliferation response among all groups, while S-HT demonstrated neither antibody maturation nor increased T cell proliferation response to Spike peptide pools. NS and non-immunocompromised participants showed both increasing neutralizing antibody levels (until a plateau ~25-30 days post symptom onset) and SARS-CoV-2-specific T cell responses.

Conclusions:

Our study demonstrated a hierarchy of immunocompromised conditions that increase the risk of delayed viral clearance and SARS-CoV-2 evolution, with the highest risk in those with severe hematologic malignancy/transplant. The findings may be explained by the suppression of both SARS-CoV-2-specific B and T cell responses.

Clinical:

(M) Clinical Manifestations and Outcomes of SARS-CoV-2, Including Long COVID, and Mpox Infections

Search Terms:

Immunity
Immunocompromised
Immunodeficiency
SARS-CoV-2
SARS-CoV-2 vaccination

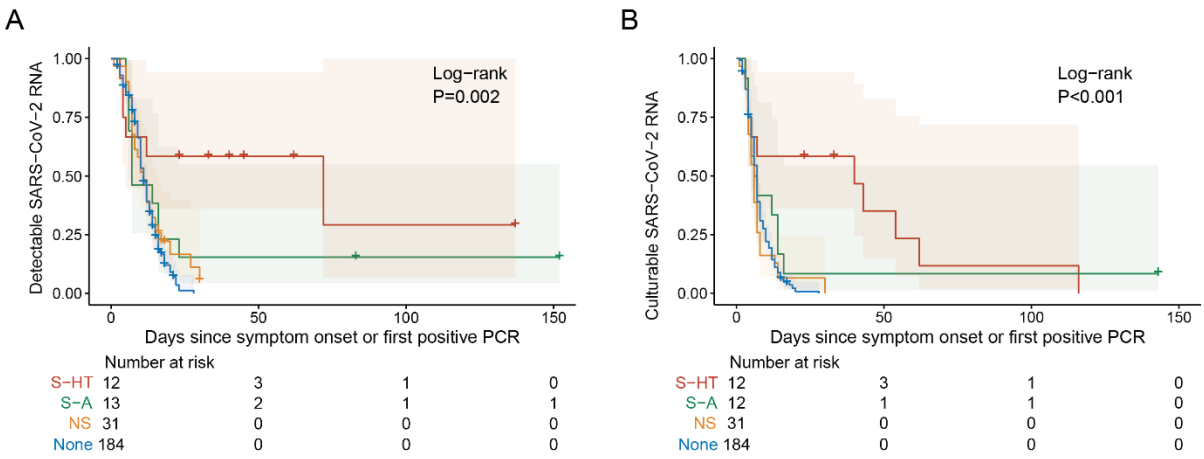

Figure 1. Kinetics of SARS-CoV-2 viral RNA and culturable virus among different immunocompromised groups. A, Kaplan-Meier estimates of upper respiratory viral clearance (viral load below lower level of quantification). B, Kaplan-Meier estimates of upper respiratory culturable virus clearance.

Multimodal Assessment of Antigen Persistence in the Post-Acute Phase of SARS-CoV-2 Infection

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138

Abstract Type:

General Abstract Submission

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Background:

Although RNA viruses like SARS-CoV-2 are considered transient, viral components can persist beyond the acute phase due to various virologic and immunologic factors. Recent studies have suggested that SARS-CoV-2 antigens may persist following COVID-19 but were limited by a lack of comparison to true negative control samples.

Methods:

We assessed viral persistence in two ways: (1) Single molecule array (Simoa) assays for SARS-CoV-2 spike, S1, and nucleocapsid antigen in plasma from 171 individuals in the post-acute phase of SARS-CoV-2 infection and 250 pre-pandemic control samples, and (2) RNAscope assessing SARS-CoV-2 spike RNA in situ in rectal tissue obtained via flexible sigmoidoscopy in 5 individuals between 90 and 676 days post-COVID (without reinfection), with H&E and immunohistochemical visualization of CD3 and CD68 to localize viral RNA signals within tissue regions and immune cell types.

Results:

In plasma, compared to the proportion of antigen positivity in pre-pandemic controls (2.0%), detection of any SARS-CoV-2 antigen was more frequent across all post-acute COVID-19 time periods (3-6 months: 12.6%, $p<0.001$; 6-10 months, 10.7%, $p=0.0002$; 10-14 months, 7.5%, $p=0.017$; (a)). These differences were driven by spike for up to 14 months and nucleocapsid in the first 6 months after infection. Hospitalization for acute COVID-19 was associated with detectable antigen in the post-acute phase (OR 2.27, $p=0.054$) and strongly associated with detectable N antigen (OR 11.82, $p=0.001$).

In gut, RNAscope revealed readily detectable SARS-CoV-2 RNA in multiple cells from all rectal tissue regions surveyed from 4/5 individuals (b), except for one who had rare RNA+ cells detected in 1/3 regions. Nearly all RNA+ cells were detected in the lamina propria, without an epithelial signal. A small percentage of RNA+ cells expressed CD68, a monocyte marker, but many RNA+ cells did not express CD68 and none expressed CD3. In 3/4 samples with readily detected RNA, the signal was associated with macrophage-dense areas.

Conclusions:

Our findings provide strong evidence that SARS-CoV-2 antigens can persist beyond the period of acute illness. The observation that 7-13% of plasma samples for over a year following initial SARS-CoV-2 infection contain detectable viral antigens, which are potentially immunogenic, has significant implications given the sheer number of people infected with SARS-CoV-2 to date. Work to determine if persistent antigen contributes to post-acute sequelae such as Long COVID is needed.

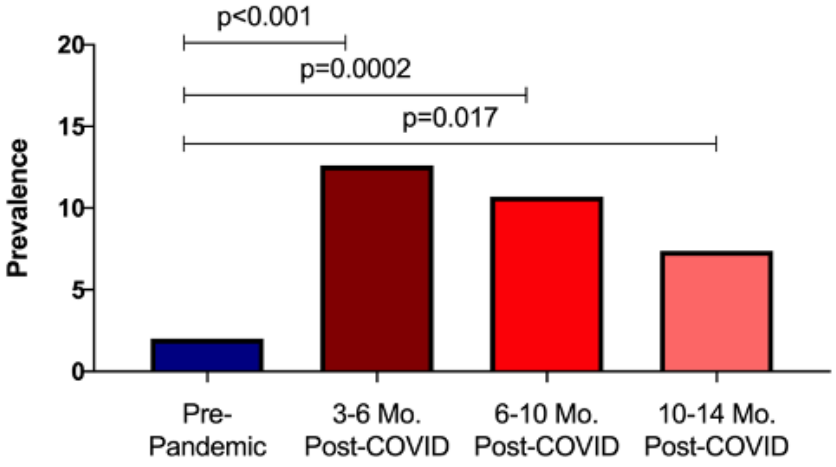
Clinical:

(M) Clinical Manifestations and Outcomes of SARS-CoV-2, Including Long COVID, and Mpox Infections

Search Terms:

Long COVID
Persistence
Post-acute COVID-19 syndrome
SARS-CoV-2
Viral reservoir

a) Prevalence of SARS-CoV-2 antigen (Spike, N, or S1) detection in true negative versus post-COVID samples.



b) Representative slide showing SARS-CoV-2 Spike RNA detected in gut lamina propria in association with CD68+ cells 2 years post-COVID using RNAscope and immunohistochemistry.