Intersecting Infections: The enhancing effect of *Neisseria gonorrhoeae* pathogenesis on HIV-1

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Running Title: *N. gonorrhoeae* pathogenesis and HIV-1

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Keywords: *N. gonorrhoeae, HIV-1, co-infection, synergy, transmission*

Word Count: 4220

Conflicts of Interest: There are no conflicts of interest to be declared.

Funding Acquisition: NIHR Sheffield Infection and Immunity Biological Research Centre

Abstract

Despite the relatively low transmission rates of HIV-1, the virus accounted for 1.5 million new infections worldwide deaths in 2020, with widespread infection and devastating sequelae. Various mechanisms have been described which exacerbate HIV-1 progression including concurrent infection with other sexually transmitted infections (STIs). Epidemiological evidence has suggested the strongest association between *N. gonorrhoeae* and HIV-1 compared to other STIs and the presence of untreated *N. gonorrhoeae* before infection with HIV-1 has been shown to enhance viral infection. Molecular investigation has corroborated this by showing that presence of *N. gonorrhoeae* enables transmission of HIV-1 across the epithelial membrane, enhances replication of HIV-1, increases viral shedding, and heightens immune dysregulation. Gonorrhoea infections are rapidly increasing worldwide providing a potential platform for increased HIV-1 incidence. Furthermore, whilst treatment of *N. gonorrhoeae* in parallel infection alleviates HIV-1 progression and transmission, this is becoming a less viable option as the threat of multidrug resistance within *N. gonorrhoeae* proliferates. These findings highlight the requirement for greater surveillance of concurrent infections to tackle the HIV-1 epidemic and warrant monitoring of the resistance crisis in *Neisseria gonorrhoeae* to prevent worsening outcomes of HIV-1 patients.

Introduction

The World Health Organisation has stated that HIV, viral hepatitis, and sexually transmitted infections (STIs) together account for 2.3 million deaths worldwide annually (1), however, little focus is made upon their concomitant infections, and the exacerbating effect of *Neisseria gonorrhoeae* on HIV-1 infection. HIV is a complex viral infection which alters host cells indefinitely and consists of two different subtypes, HIV-1 and HIV-2. HIV-1 is responsible for most worldwide cases as it shows higher transmissibility and faster progression of disease (2). Transmission occurs through bodily fluids predominantly by sexual intercourse but also through intravenous drug use, contaminated blood products, and vertical transmission. After entry into the host, it traverses the genital mucosal barrier before binding to immune cells and initiating replication (3). This leads to the eventual destruction of CD4+ T cells, and causes significant immunosuppression and the development of acquired immune deficiency syndrome (AIDS) (3).

One of the factors that increase transmission and exacerbate disease progression is the presence of concurrent sexually transmitted infections (STIs), including infection with *Neisseria gonorrhoeae* (3). *N. gonorrhoeae*, or the gonococcus, causes the treatable bacterial infection, gonorrhoea (4). Gonococci can colonise the mucosal epithelium at multiple sites of infection including the urogenital tract, cervix, pharynx, rectum and conjunctiva (5). Infection can be symptomatic and asymptomatic with most asymptomatic cases occurring in gay and bisexual men who have sex with men (GBMSM). This was shown in the latest surveillance data from the UK with a total of 53.3% (n=936) asymptomatic cases, with 646 of these in GBMSM and 167 in women (6). Complications can occur with sustained untreated infection and can result in disseminated disease, pelvic inflammatory disorder, and infertility (5). Sex-specific presentation in males includes urethral discharge and pain during urination, and in females includes cervical inflammation and purulent discharge (4,5). Whilst infection with *N. gonorrhoeae* is

treatable with antibiotics, it is still classified as a World Health Organisation high priority pathogen due to the persistence of multidrug resistant strains (7), meaning the pathogen remains a public health threat.

For both *N. gonorrhoea*e and HIV-1, sexual transmission is the major cause of infection (2,8,9). This shared method of transmission means both infections can occur concurrently. This has been observed in studies showing that HIV-positive men who have sex with men (MSM) are four times more likely to carry an additional STI than HIV-negative MSM (10,11). Whilst all STIs demonstrate moderate to strong associations with HIV, recent modelling evidence has found *N. gonorrhoeae* has the strongest prevalence association with HIV-1, with a correlation coefficient of 0.84 (12). *N. gonorrhoeae* is also believed to increase transmission of HIV-1 both by enhancing the infectivity and susceptibility to HIV-1 in sexual partners by increased shedding, most notably in the early stages of HIV-1 infection (8).

The mechanisms by which *N. gonorrhoeae* enhances viral infection involve both direct (enhancing HIV-1 viral replication and transmission) (13,14) and indirect means (immune response activation) (15), which will be discussed in the later sections of this review. Recent breakthroughs have further established the molecular and immunological link between *N. gonorrhoeae* and HIV-1, which provides causal data to the correlational findings from clinical and modelling studies. This review aims to discuss the recent epidemiological and clinical links between *N. gonorrhoeae* before discussing some breakthrough molecular and immunological advances.

Epidemiology

The incidence of *N. gonorrhoeae* has wavered throughout the years but is inextricably linked to HIV. In the UK, the 1960s saw a rise in the “sexual liberation” countercultural movement, which was in line with a greater incidence of gonorrhoea in MSM (16).

However, as the HIV epidemic emerged in the 1980s, gonorrhoea incidence declined sharply as condom usage increased and the number of casual sexual partners diminished (1,12). ART was introduced and disseminated widely to the public in 1987 and consequently an increase in STI incidence was observed in the 1990s, which has continued to worsen throughout the 2000s (4,17). One behavioural shift that occurred because of the HIV epidemic was a concept known as “serosorting” or “negotiated safety”, where individuals would participate in unprotected sex with individuals of the same HIV status as themselves (18). However, this practice contributed to the persistence of HIV between 2000-2013 with undiagnosed individuals unknowingly transmitting to HIV-negative groups and contributed to the rise of STIs (19), although the practice of serosorting appears to have diminished in recent years (9). Currently, gonorrhoea diagnoses have more than doubled over the past 10 years in the UK going from 31,177 in 2013 to 85,223 in 2023, as well as the largest number of annual cases reported in 2023 since records began in 1918 (6).

Use of preventative medicine has also played a role in changing behavioural practices. Preexposure prophylaxis (PrEP) was introduced as a daily treatment in the UK in 2017 (20), which offered temporary protection against HIV viral replication. PrEP was found to decrease HIV acquisition in the UK (6), but evidence indicated an association with increased STI prevalence, potentially caused by diminished condom use in PrEP users (18). In Germany, a study found that STI prevalence in MSM was high, particularly in PrEP users compared to non-PrEP users (21). Another US based study found a 14% increase in STI diagnoses in patients after PrEP use compared to before PrEP use, however this may have been caused by increased screening during the period examined (22). Additionally, a large study conducted in Australia (n=2981) found that STI prevalence increased after enrolment on to PrEP, with 1242 incidences of *N. gonorrhoeae,* and 39.0 incidence rate per 100 person years. Interestingly, only 736

individuals accounted for the majority these cases. This suggests repeated infection amongst the same individuals during the 1.1-year period of the study, meaning high STI incidence was confined within a subset of individuals, rather than the whole of the GBMSM population (23).

At present, the World Health Organisation has found that 1.5 million individuals were newly diagnosed with HIV globally in 2020 (1). Whereas, for gonorrhoea 82.4 million people were newly diagnosed (1) (Figure 1). The worldwide proportion estimated to exhibit two concurrent STIs is 37.7% (12). A recent meta-analysis of dual infection by Zhang *et al.,* claimed that only 0.8% of cases exhibited both *N. gonorrhoeae* and HIV-1 based on worldwide data, but this number has been disputed.

In their meta-analysis, Zhang and co-workers demonstrated a clear diversity between different economic zones, with 0.3% of co-infection cases in high-resource settings (HRS) contrasting with 1.3% in low-resource settings in 2024 (24). However, this analysis may not be an accurate reflection of trends in HRS from surveillance reports, which suggest a higher number of concurrent *N. gonorrhoeae* and HIV-1 cases. The gonococcal resistance to antimicrobials surveillance programme (GRASP) conducted across the UK suggested 9.4% of positive gonorrhoea cases (n=1,762) were associated with those living with HIV in 2024 (6), while other reports have suggested a 3.9% prevalence of co-infection in men who have sex with men (MSM) across England in 2021 (25), which is significantly higher than the 0.3% claim from Zhang *et al.,* in HRS.

Figures also vary across geographical regions, in Europe for example, the prevalence of co-infection was 0.6% which contrasted starkly with 12.9% in Central Africa (24). However, the World Health Organization has described barriers with the availability of sexual health data in Africa, which suggests these figures may be higher than stated. This is in part due to the stigma of being diagnosed with an STI in areas of Africa, which is reflected in the politics and culture of the continent. Twelve of the twenty-five Central

and West African countries have criminalised same-sex relationships, and twenty-one have criminalised sex work (1). These policies no doubt act as a deterrent to groups that are most vulnerable to STIs, MSM, transgender people, and sex workers, in jeopardising themselves to seek treatment (26).

Global surveillance of concurrent *N. gonorrhoeae* and HIV-1 is lacking but would provide further insights into trends across regions with greater clarity. However, findings from GRASP and meta-analyses show that the dynamics of co-infection with *N. gonorrhoeae* and HIV-1 are complex, involving not only biological factors but also sociological, economic and behavioural factors (6,24). This includes the number of sexual partners, history of addiction, sexuality, access to sexual health services, and education of safe sexual practices (27).

Viral Shedding

One proposed biological link between *N. gonorrhoeae* and HIV-1 is that *N. gonorrhoeae* enhances transmission of the virus through increased HIV-1 shedding. This has been established in both humans and in non-human animals. In 2018, a humanised mouse model was produced by engrafting immunodeficient mice with CD34+ stem cells. Mice were exposed to HIV-1 and infection was confirmed by increased viral load observed in blood after four weeks. However, after mice were infected with *N. gonorrhoeae* the overall viral load remained constant, but viral shedding increased in the genital tract, in line with clinical data in humans (28). This suggests *N. gonorrhoeae* enhances HIV-1 infection by increasing transmissibility of the virus through increased shedding.

Increased shedding has also been observed in studies monitoring co-infection of both sexes in humans. In females with concurrent infection, cervicovaginal viral shedding was significantly higher in those who were also infected with *N. gonorrhoeae.* Treatment of *N. gonorrhoeae* with antibiotics decreased viral shedding from 42% to 21%,

demonstrating that treatment drastically reduced transmission (29). In males, those infected with *N. gonorrhoeae* and HIV-1 had eight times higher levels of HIV-1 RNA in their semen compared to HIV-1 positive men without *N. gonorrhoeae* (30). Later studies found similar evidence, with fivefold greater levels of viral RNA found in the semen of men with concurrent HIV-1 and *N. gonorrhoeae* (31), a factor linked with greater transmissibility of the virus (32). Findings also suggest that higher seminal viral loads are diminished after treatment with antibiotics, suggesting that tackling the high prevalence of *N. gonorrhoeae* should be considered in efforts to reduce HIV-1 transmission (12,30,31). However, the increasing threat of multi-antibiotic resistant *N. gonorrhoeae* strains may jeopardise this, increasing HIV-1 transmissibility.

There is evidence that has suggested that highly virulent, antibiotic resistant strains of *N. gonorrhoeae* were associated with HIV status, but conflicting research on the topic means a clear link has not been fully established. A large-scale survey conducted in 2009 in Thailand analysed *N. gonorrhoeae* isolates that were collected from HIV-positive patients, and antimicrobial resistance (AMR) was determined using disk diffusion assays. None of the 122 isolates were susceptible to penicillin or tetracycline and 90% of the isolates were resistant to ciprofloxacin. 83.6% of the isolates produced β-lactamase, and 79.5% of these were also resistant to tetracycline (33). Further evidence into the virulence of *N. gonorrhoeae* isolates using sequencing data suggested a link between specific subspecies of *N. gonorrhoeae* found in HIV-positive cases in Australia. *Neisseria gonorrhoeae* molecular antigen sequence typing (NG-MAST) is a scheme which is used to categorise *N. gonorrhoeae* subtypes by comparing two variable genes (*porB* and *tbpB*). NG-MAST data from 3340 *N. gonorrhoeae* isolates showed that HIV notifications were linked to 65 different *N. gonorrhoeae* genotypes. Two sequence types (STs) were commonly associated with HIV, ST-1407 and ST-2992, and both demonstrated resistance to penicillin and azithromycin from a study in Australia (34).

194 However, conflicting evidence from England found no such link between antimicrobial
195 resistance (AMR) status of *N. gonorrhoeae* isolates and HIV-1 (35), but a smaller number
196 of cases was studied compared with the Australian study (34). This suggests further
197 surveillance is warranted to firmly establish a link between highly virulent *N. gonorrhoeae*
198 strains and HIV-1.

199 **Transmission of HIV-1 across the membrane**

200 After infection with HIV-1 the virus traverses the epithelial membrane to begin replication
201 within cells and initiate seroconversion. Up until 2022, the mechanisms for HIV-1
202 traversal across the membrane were not firmly established, with most researchers
203 suggesting that HIV-1 passively traversed disrupted epithelial junctions (36,37). A
204 mechanism for HIV-1 transcytosis across an intact epithelial membrane found that HIV-
205 1 used a cervical membrane receptor to traverse the epithelium. These findings showed
206 a closer connection to HIV-1 and *N. gonorrhoeae* than previously assumed, as both
207 pathogens used complement receptor 3 (CR3) for transcytosis across the cervical
208 mucosal barrier (38) (Figure 2). In addition, the presence of *N. gonorrhoeae* was shown
209 to enhance transmission of HIV-1 across cervical mucosa, which saw a 55% increase
210 when cervical tissues were exposed to *N. gonorrhoeae* after 24 hours, and a 350%
211 increase in transmission after 7 days of exposure (15), suggesting that CR3 activation
212 by gonococcal pili allows for more efficient HIV-1 binding (39). This shows that HIV-1
213 and *N. gonorrhoeae* have shared methods of transcytosis, with a compounding effect on
214 one another.

215 **Immune cell responses**

216 CD4+ T cells

217 HIV-1 replicates in CD4+ T cells meaning CD4+ T cells play a significant role in HIV-1
218 infection. This is facilitated by defensins, molecules that are enhanced by infection with

N. gonorrhoeae. Human defensins 5 and 6 (HD5, HD6) are defence peptides that are expressed by secretory cells, and have been observed in elevated levels when cervical cells are exposed to *N. gonorrhoeae* (13). HD5 and HD6 were found to increase infectivity of HIV-1 by enhancing attachment and the concentration of the virus to CD4+ T cells, promoting entry and replication in the presence of *N. gonorrhoeae* (40). The mechanisms by which HD5 and HD6 increase infectivity is related to the structure of the peptides, as loss of intramolecular cysteine bonds prevented the enhancing effect. When the cysteine bonds were present HD5 and HD6 had an aggregating effect on HIV-1 to CD4+ T cells shown in microscopy images. However, the enhancing effect of *N. gonorrhoeae* only occurred if the cells were pre-treated with it before HIV-1 infection. This suggests that enhancement of HIV-1 is reliant on HD5 and HD6 presence before HIV-1 initiates infection (13).

To investigate the mechanisms of co-infection in CD4+ T cells Ding *et al.*, (2010) exposed primary resting CD4+ T cells to *N. gonorrhoeae* peptidoglycan, as peptidoglycan is a known TLR2 agonist, the findings showed enhanced HIV-1 viral replication (14). During co-infection, known TLR2 pathways were activated, suggesting TLR2 activation by *N. gonorrhoeae* was crucial for viral enhancement. However, TLR2 activation did not enhance HIV-1 infection after the early stages of infection, which suggests that the enhancing effect of *N. gonorrhoeae* only occurs if the individual is already infected with *N. gonorrhoeae* or becomes exposed to *N. gonorrhoeae* in the early stages of HIV-1 infection. Additionally, IL-2 was a necessary cytokine for *N. gonorrhoeae* mediated enhancement of HIV-1, as HIV-1 enhancement only occurred in the presence of IL-2 and TLR2 agonists. Absence of IL-2 during these early infection stages inhibited viral replication, suggesting an importance for this cytokine during co-infection (14). This suggests that IL-2 that is expressed during *N. gonorrhoeae* infection plays a role in enhancing HIV-1 pathogenesis (41).

Further, studies utilising immortalised CD4+ cell lines have suggested gonococcal infection can increase transcription of HIV-1 genes. One of the ways in which HIV-1 transcription is controlled is by activation of a 636 base pair region within the HIV-1 RNA genome known as the long-terminal repeat (LTR) region. This region promotes HIV-1 replication when activated (42). Jurkat cells transformed with a luciferase reporter gene under the control of a LTR HIV-1 promoter were infected with *N. gonorrhoeae*. Increased luciferase activity was observed after the cells were infected with *N. gonorrhoeae*, suggesting increased transcription of HIV-1 within cells after *N. gonorrhoeae* exposure (43).

Genome-wide mutagenesis studies of *N. gonorrhoeae* demonstrated that mutation within the hldA locus could inhibit HIV-1 transcription within Jurkat cells. This increased HIV-1 mechanism has been linked with the *hldA* locus from *N. gonorrhoeae*. *hldA* encodes the heptose phosphate kinase enzyme which is responsible for liberating a heptose molecule during the growth phase of *N. gonorrhoeae.* Heptose is a carbohydrate used by *N. gonorrhoeae* for synthesis of surface lipooligosacharide molecules, a critical component of the bacterial outer membrane. The liberated heptose molecule activated CD4+ T cells and initiated the NF-kB dependent transcription of HIV-1 LTR (44). NF-kB are a group of proteins that bind to DNA to regulate transcription. When *N. gonorrhoeae* binds to epithelial cells through TLR2 the NF-kB signalling pathway is initiated, resulting in increased expression of pro-inflammatory cytokines (45). NF-kB also controls HIV-1 transcription by binding to the LTR region of HIV-1, eliciting replication of HIV-1 virions (42). Interestingly, this function of *N. gonorrhoeae* is unique, as heptose is expressed in other bacteria including *E. coli* but does not elicit the same enhanced transcriptional response as *N. gonorrhoeae* (44).

Critics of these studies suggest it relied on immortalised cell lines to investigate the effect of *N. gonorrhoeae* on HIV-1 infection as other studies have found differential responses

in co-infection between primary human CD4+ T cells compared to Jurkat cells. Whilst both cell types produced a significant cytokine response upon exposure to *N. gonorrhoeae*, Jurkat cells showed increased viral replication within the cell, but in primary CD4+ T cells there was an inhibition of viral replication (46). This suggests some cell lines, such as Jurkat cells, produce a false positive result regarding HIV-1 and *N. gonorrhoeae* co-infection. However, it does not explain why HIV-1 replication was increased in primary CD4+ T cells in previous studies Ding *et al.*, (2010) (14) and were concordant with data from Chen *et al.*, (2003) (43) who used a Jurkat cell line derivative.

CD3+ T cells

Whilst CD4+ T cells remain the preferential immune cell for progression of HIV-1 infection (47), some argue that systemic immune response is a more important marker for HIV-1 risk (48). This was shown in a paper by Sanyal *et al.*, (2019) which found that CD3+ T cells were integral in the transmission of HIV-1 across the cervical membrane in a cervical tissue model (15). Cervical epithelial membrane ruffling caused by *N. gonorrhoeae* infection leads to migration of CD3+ T cells to the subepithelial layer, and higher levels of IL-1β and TNF-α cytokines. The flooding of CD3+ T cells to the subepithelial layer of the cervical model provided greater levels of HIV-1 target cells which lead to higher levels of HIV-1 replication during co-infection. Therefore, both CD4+ and CD3+ T cells play an important role in enhancing HIV-1 infection during *N. gonorrhoeae* infection, warranting further investigation of a more systemic T cell response to explain how *N. gonorrhoeae* enhances HIV-1 infection. A limitation of this study is the low sample size (n=14), meaning there is scope to expand this study investigating models made from cervical tissues from donors of different ages, menstrual cycles and race (15). Additionally, there are large areas of uncertainty in HIV-1 and *N.*

gonorrhoeae co-infection in male uroepithelial cells, as research on male 3D models has not yet been published, highlighting a significant gap within the literature.

Dendritic cells

In addition to recruitment of T cells, *N. gonorrhoeae* has shown to enhance infection by using dendritic cells (DCs). DCs play a role in the capture of pathogens followed by antigen presentation which elicits an adaptive immune response (49). DCs have been found to capture HIV-1, acting as reservoirs of the virus, before carrying the virions to target CD4+ T cells (50). Therefore, DCs play a crucial role in enhancing infection of HIV-1, even before co-infection is involved. During co-infection, *N. gonorrhoeae* can dysregulate the adaptive immune response to enhance its own pathogenesis as well as HIV-1. This is achieved by preventing DCs in building a cytotoxic immune memory against HIV-1, and by suppressing maturation of DCs. The mechanisms of this involve *N. gonorrhoeae* binding to carcinoembryonic antigen related cellular adhesion molecule-1 (CEACAM-1) found on the surface of DCs through gonococcal outer membrane opacity (Opa) proteins. Binding of Opa to CEACAM-1 elicits an immunosuppressive response which is characterised by upregulation of IL-10 and Programmed Death Ligand 1 (PD-L1), and thereby suppressing maturation markers on DCs, such as CD38 (49,51). These effects combined mean *N. gonorrhoeae* enhances infection of HIV-1 in a mutually beneficial subversion of the immune response.

Presence of *N. gonorrhoeae* has also been found to enhance HIV-1 replication in monocyte derived DCs. Greater levels of viral DNA were found in monocyte derived DCs that were exposed to *N. gonorrhoeae* peptidoglycan, indicating further uptake of HIV-1 in DCs in the presence of *N. gonorrhoeae*. The mechanism of this response was believed to involve TLR2, as DCs without TLR2 were not enhanced (52). Meaning *N. gonorrhoeae* enhanced viral replication in DCs using TLR2 related pathways, in a similar method to the mechanisms of viral replication in CD4+ T cells described previously.

Conclusion

The dynamics of coinfection have proven to exhibit complexity, affected by several behavioural and biological factors. Eradicating the HIV-1 pandemic will therefore involve addressing the virus on multiple fronts, including acknowledgment of the enhancing effect *N. gonorrhoeae* has on HIV-1 infection. Addressing the socio-behavioural barriers that restrict access to treatment, particularly in the groups most affected, such as GBMSM, sex workers, and transgender people would help alleviate the progression of both STIs and HIV. The UK has produced up to date surveillance of STIs in specific areas (6), but worldwide surveillance could be improved, with gaps observed in some regions caused by both economic and political barriers (1). Whilst clinical reports suggest a preliminary link between *N. gonorrhoeae* and HIV (31) it is challenging to establish causality with confounding variables potentially affecting the correlation. Early *in vitro* immunological studies produced conflicting results, impacted by a lack of representative models. However, more recent work using organ culture, animal, and 3D models has shed insights into how transmission and replication of HIV-1 is enhanced when *N. gonorrhoeae* infection is present before HIV-1 entry or during the early stages of HIV-1 infection (15). This link between increased HIV transmissibility and infectivity during concurrent infection is worrying at a time when gonorrhoea incidence is rising globally alongside a concerning rise in antimicrobial resistance within *N. gonorrhoeae*. It is therefore critical to monitor these cases and utilise these results to develop novel drugs or repurpose existing medications to treat co-infections and prevent worsening the HIV-1 crisis (53).

Acknowledgments

This study/research is funded by the National Institute for Health and Care Research (NIHR) Sheffield Biomedical Research Centre (NIHR203321). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

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Table 1. A spread of co-infection point-prevalence (%) for HIV-1 and N. gonorrhoeae based on different regions.

This table demonstrates the heterogeneity observed between figures for co-infection across several papers (8,21–28). Whilst the year of data collection and groups studied differ in some examples, significant variation is observed, even within the same continent and region - highlighting the requirement for comprehensive global surveillance of co-infection.

Continent	Region and co-infection point prevalence	Authors	Risk group	Reference	Year of data collection
Asia	Asia – 2.3%	Zhang., *et al*	M&F	(27)	2025
	Delhi, India – 7.0%	Bala., *et al*	M	(28)	2011
	Shiraz, Iran – 2.9%	Ghassabi., *et al*	M&F	(29)	2018
Europe	Europe – 0.6%	Zhang., *et al*	M&F	(27)	2025
	UK – 9.4%	GRASP	M&F	(7)	2024
	England – 12.53%	O'Brien., *et al*	M&F	(20)	2012-2013
	Barcelona – 7.7%	Sentís., *et al*	15-24 year old M	(30)	2015
	Barcelona – 1.6%	Sentís., *et al*	15-24 year old F	(30)	2015
Africa	Central Africa – 12.9%	Zhang., *et al*	M&F	(27)	2025
	East Africa – 2.6%	Zhang., *et al*	M&F	(27)	2025
	Kenya – 17.0%	Sheung., *et al*	F sex workers	(31)	2008
Oceania	Oceania – 13.5%	Zhang., *et al*	M&F	(27)	2025
	Australia – 37.7%	Callander., *et al*	M	(32)	2017
North America	North America – 0.3%	Zhang., *et al*	M&F	(27)	2025
	Toronto, Ontario – 1.2%	Grewal., *et al*	MSM	(33)	2010-2013
South America	South America – 0.6%	Zhang., *et al*	M&F	(27)	2025
	Brazil – 5.2%	Cunha., *et al*	MSM	(34)	2015

Table 2. Shows a comparison of 4 different studies and levels of reported increase of HIV-1 viral RNA after exposure to N. gonorrhoeae.

This table shows viral RNA significantly increases during when exposed to both HIV-1 and *N. gonorrhoeae*, which can explain the increase in viral shedding during concurrent infection.

Model type	Effect of *N. gonorrhoeae* on HIV-1 viral RNA shedding	Further background of study	Reference
Mouse - female	Significantly increased	7 out of 9 (78%) mice exhibited vaginal shedding after *N. gonorrhoeae* infection compared to only 2 out of 7 (29%) in the PBS control group.	(43)
Human – female sex workers	Adjusted odds ratio of 1.9	1202 female sex workers were investigated for factors that increase vaginal shedding. *N. gonorrhoeae* increased risk of shedding by the adjusted odds ratio of 1.9. When the STI was treated vaginal shedding decreased from 42% to 21%.	(44)
Human – male	8-fold higher	135 men from Malawi showed a strong association with higher levels of HIV-1 in the semen ($15.8x10^4$ copies/ml). This decreased to $8.91x10^4$ copies/ml after treatment of the STI.	(45)
Human – male	5-fold higher	13 cases of GBMSM showed that the mean log semen plasma viral loads were higher for those with *N. gonorrhoeae* and *Chlamydia trachomatis* infection (4.27) compared to the controls (3.55). After treatment with antibiotics mean semen plasma levels dropped by 0.25 log.	(46)

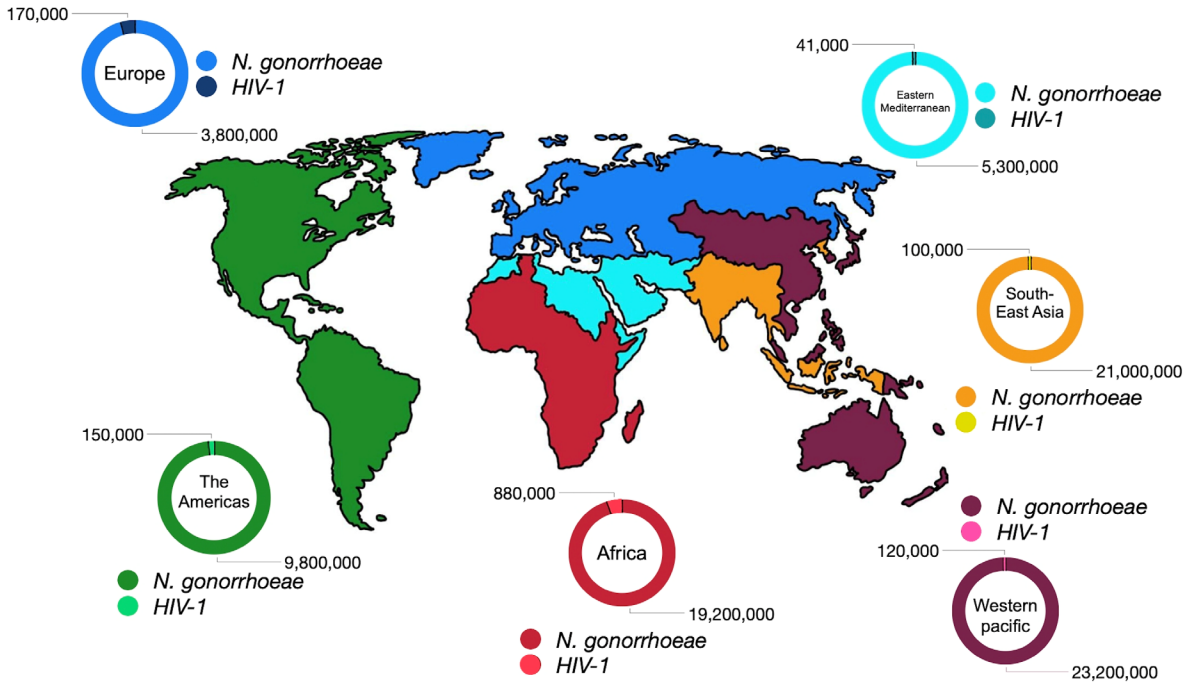

Fig 1. A worldwide map showing the incidence of HIV-1 and N. gonorrhoeae infections in 2021.

Generally, higher incidence of gonorrhoea reflects higher HIV-1 incidence. The African region is disproportionately affected by HIV incidence with numbers five times greater than the European region. Figures were taken from the 2021 WHO STI report (1).

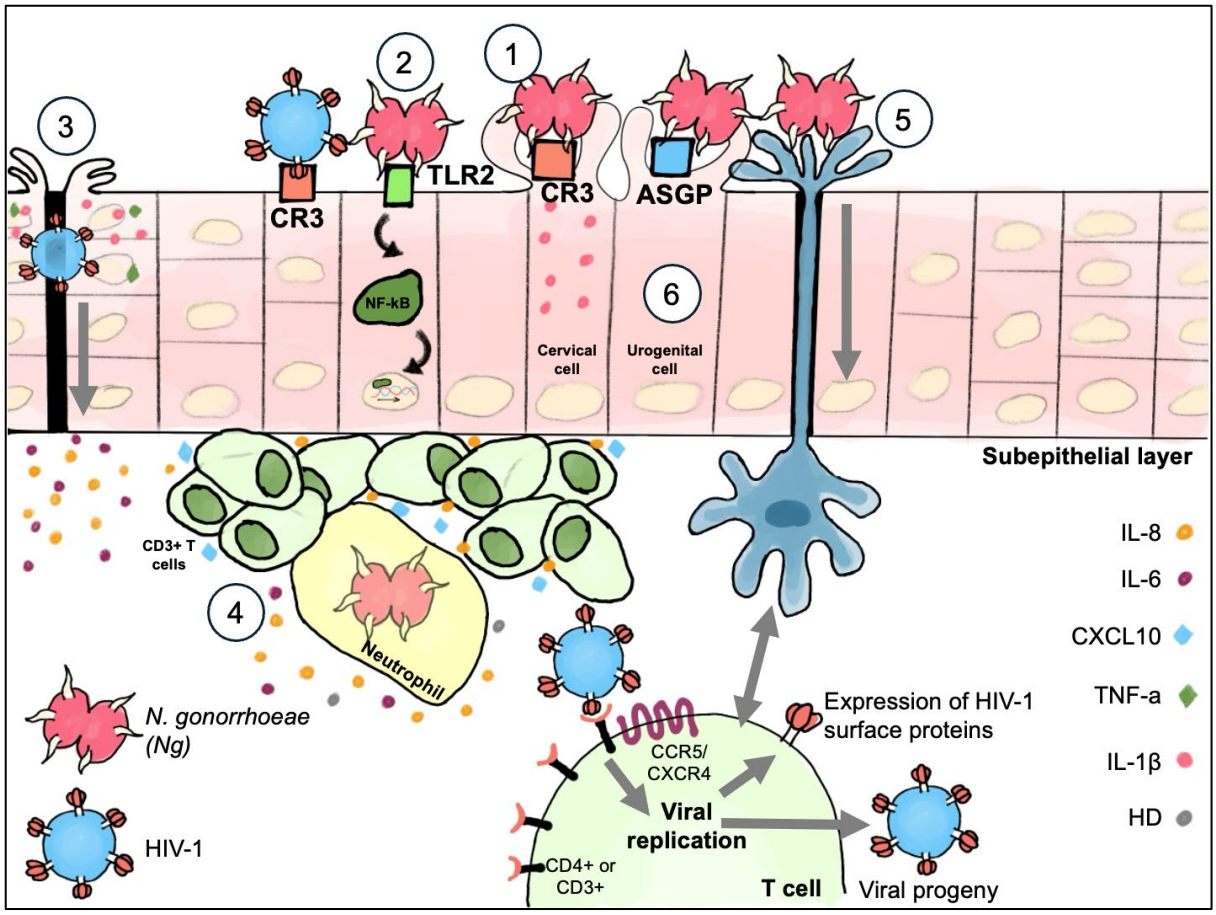

Fig 2. Enhanced transmission, and replication of HIV-1 caused by N. gonorrhoeae infection.

1) *HIV-1 and Ng both use CR3 for transcytosis. Binding of Ng to CR3 leads to secretion of IL-1β within the epithelial cell, activating CXCL10 and IL-8 chemokine and cytokine production (15). The cytokines and chemokines attract CD3+ T cells to the subepithelial layer so that sub-mucosal HIV can infect these target cells resulting in greater levels of HIV-1 replication.* ***2)*** *TLR2 recognition by Ng activates downstream signalling of NF-kB. This produces increased pro-inflammatory cytokines (14,45).* ***3)*** *Membrane ruffling induced by Ng allows for HIV-1 transport through epithelial lesions (15). Once HIV-1 enters the mucosal space it initiates viral replication within T cells.* ***4)*** *Activated neutrophils increase levels of pro-inflammatory cytokines and human defensins (HD). These have both been found to increase levels of HIV-1 replication*

(36,45). ***5)*** *Binding of Ng to DCs elicits immune dysregulation and immune system suppression that enhances both Ng and HIV-1 infection (52). DCs also facilitate transport of Ng though epithelial lesions, Ng is moved from the surface of the epithelium to the subepithelial layer where Ng binds to DCs (27).* ***6)*** *Ng enters male epithelial cells using the ASGP receptor. However, very little is still known about transcytosis of HIV-1 in male urogenital cells. There is a possibility that HIV-1 enters the submucosal space via a specific receptor found on male epithelial cells, but this knowledge currently remains an enigma. Development of 2D and 3D male models would benefit understanding of HIV-1 transcytosis and co-infection.*