Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Review article: Biomedical intelligence | Published 26 January 2018 | doi:10.4414/smw.2018.14580
Cite this as: Swiss Med Wkly. 2018;148:w14580

Preventing HIV transmission through blockade of CCR5: rationale, progress and perspectives

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Summary

Of the two million people estimated to be newly infected with human immunodeficiency virus (HIV) every year, 95% live in poorer regions of the world where effective HIV treatment is not universally available. Strategies to reduce the spread of HIV infection, which predominantly occurs via sexual contact, are urgently required. In the absence of an effective vaccine, a number of approaches to prevent HIV infection have been developed. These include using potent anti-HIV drugs prophylactically, either through systemic administration or topical application to the mucosal tissues that HIV initially encounters during sexual transmission. Genetic deficiency of the chemokine receptor CCR5 provides individuals with a remarkable degree of protection from HIV acquisition. This is because CCR5 is the major coreceptor used by HIV to infect new target cells. Since CCR5 deficiency does not appear to carry any health disadvantages, targeting the receptor is a promising strategy for both therapy and prevention of HIV.

In this review we first describe the advantages and limitations of the currently available strategies for HIV prevention, then we focus on strategies targeting CCR5, covering the progress that has been made in developing different classes of CCR5 inhibitors for prophylaxis, and the perspectives for their future development as new weapons in the global fight against HIV/AIDS.

Key words: *HIV/AIDS prevention, PrEP, microbicide, CCR5*

Rationale

Current status of the HIV epidemic and principal transmission mechanisms

According to the latest estimates (aidsinfo.unaids.org), 37 million people are currently living with human immunodeficiency virus (HIV), with two million people newly infected every year. HIV/AIDS disproportionally affects the poorer regions of the world where ~95% of people living with HIV can be found, and a similar proportion of the new infections occur. The situation is particularly severe in sub-Saharan Africa, with ~70% of all cases.

HIV transmission can occur (i) through blood-to-blood contact (transfusion, needle sharing, needle stick), (ii) from mother-to-child (during pregnancy, childbirth or breast-feeding), and (iii) as a consequence of unprotected sexual intercourse, which accounts for the vast majority of new HIV infections in the world (aidsinfo.unaids.org).

Progress with HIV therapy: optimised combined antiretroviral therapy

Until the mid-1990s, use of the relatively few licensed HIV therapeutics was hampered by their low potency, poor bioavailability and pharmacokinetics, toxic side-effects and the rapid emergence in patients of drug-resistant strains [1], and HIV was regarded as an almost universally fatal disease. The advent of new antiviral medicines and improved strategies for their use have transformed the situation, with HIV now considered as a manageable chronic illness [2].

Today, more than 25 different anti-HIV drugs are approved for clinical use, classed according to the step in the viral life cycle that they inhibit: nucleoside-analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase inhibitors, protease inhibitors, fusion inhibitors and coreceptor antagonists [3]. Optimised HIV therapy (known as combined antiretroviral therapy) involves administration of selected combinations of anti-HIV drugs (normally two NRTIs in combination with an NNRTI, an integrase inhibitor or a protease inhibitor), together with regular clinical follow-up to monitor treatment efficacy, side-effects and the emergence of viral escape mutants [4, 5]. Not only does combined antiretroviral therapy suppress viral replication to a level where infected individuals can live essentially free of symptoms [6], but it has also been shown to strongly reduce onward transmission of the virus, providing a clear rationale for treatment of HIV-infected individuals as a means of preventing the spread of the epidemic [7].

Beyond therapy: treatment as prevention

Expanding global access to optimised combined antiretroviral therapy has been put forward as a strategy to end the epidemic by 2030 [8]. Such a venture would be hugely challenging to undertake, however, not only in terms of providing the required diagnostic tests and anti-HIV drugs for many millions of people over many years, but also in terms of upgrading healthcare infrastructure to ensure adequate monitoring. An additional problem relates to the social stigma attached to HIV-positive status in many of

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the regions at the centre of the epidemic, which negatively impacts campaigns for both testing and treatment of HIV [9–11]. For this reason, the development and adoption of complementary approaches to prevent transmission of HIV from person to person remains a priority. To make an impact, any such approach must be safe enough for use in uninfected people, inexpensive enough to be economically feasible, acceptable enough to ensure sufficiently broad uptake in the population, and designed in such a way as to minimize interference with the procedures used to treat infected people.

No effective HIV vaccine in the near future

The genetic variability of HIV and its capacity to evade the immune system has made the effort to develop an effective HIV vaccine immensely challenging. Hundreds of clinical trials of HIV vaccine candidates have been undertaken, leading to six large-scale clinical trials for different vaccine concepts, none of which showed sufficient efficacy to be approved for clinical use [12–14]. Progress continues to be made, using both theoretical and empirical approaches to vaccine design [13], but it is generally accepted that many more years will be required to develop a suitable HIV vaccine. In the meantime, several other HIV prevention strategies are being elaborated.

Barrier protection for HIV prevention

Condoms can be used not only to prevent HIV transmission but also other sexually transmitted diseases and unwanted pregnancies. When used consistently and correctly, male condoms have been estimated to be between 60% and 80% effective at preventing HIV transmission [15, 16]. Although condoms represent a key component of the HIV prevention arsenal, initiatives to make their use more widespread and consistent are hampered not only by issues of cost and supply, but also those of acceptability including (i) contraceptive activity, (ii) social stigma, (iii) moral or religious objections, and (iv) concerns about impact on sexual pleasure [17].

Male circumcision

The male foreskin provides a surface that can facilitate the acquisition of a range of sexually transmitted pathogens, including HIV [18]. Three clinical trials conducted in Africa demonstrated that male circumcision reduces HIV acquisition from women to men by approximately 60% [19–21], resulting in a joint policy statement from the World Health Organisation and UNAIDS that endorses male circumcision as an approach for HIV prevention [22]. An observational study of a sample of sexually active men in the USA indicated a lower HIV infection rate among circumcised individuals [23], suggesting that the conclusions drawn from the studies carried out in Africa are also applicable to populations elsewhere. It should be noted, however, that the protective benefit to circumcised men is not extended to their sexual partners [24–27].

Pre-exposure prophylaxis

During the 1980s and 1990s, anti-HIV drugs began to be used successfully both in post-exposure prophylaxis, where establishment of infection is prevented by the prompt administration of drugs after a known exposure to the virus [28, 29], and in the prevention of mother-to-child transmission of HIV, where drugs are administered to the mother in the period up to and during birth [30, 31]. At that time, use of anti-HIV drugs to prevent infection of healthy individuals at risk of exposure (referred to as pre-exposure prophylaxis, or PrEP) was not considered feasible owing to concerns about low potency, high toxicity, complicated dosing procedures and the emergence of drug resistance [32].

Oral pre-exposure prophylaxis with TDF-FTC

This perception changed with the approval of two new HIV therapeutics with improved potency and safety profiles: the NRTI tenofovir disoproxil fumarate (TDF, marketed as Viread®) in 2001 [33], and TDF in combination with a second NRTI, emtricitabine (TDF-FTC, marketed as Truvada®), in 2004 [34]. These drugs were rapidly developed for clinical evaluation in PrEP, and several phase III trials involving TDF and TDF-FTC products have now been carried out. TDF-FTC provided statistically significant reductions in HIV infection events in three separate studies in transgender women and men who have sex with men [35–37]. A study with TDF-FTC in a population of intravenous drug users showed a comparable protective benefit [38], and two trials in populations of heterosexual men and women showed statistically significant efficacy [39, 40].

Limitations of TDF-FTC-based oral pre-exposure prophylaxis

Although TDF and TDF-FTC-based PrEP has emerged as a significant breakthrough in the fight against HIV/AIDS [41], it should be noted that two other large-scale trials, both conducted with women at sites in Africa, failed to show efficacy [42, 43]. The main explanation put forward for these trial failures was low adherence to the daily dosing regimen owing to doubts about the efficacy of the products, and social stigma related to HIV status [43], but it has also been observed that during dosing of TDF-FTC products, lower drug concentrations are achieved in vaginal tissue than in rectal tissue, another potential factor in the lower performance of the trials that specifically addressed protection of women [44].

Topical prevention: a first generation of broad-spectrum "microbicides"

During the development of the oral PrEP strategies, topically applied HIV prevention strategies were being pursued in parallel. A first group of products to reach clinical trials were vaginal gels containing simple substances that had been shown to possess some anti-HIV activity *in vitro*: (i) detergent-based spermicides, (ii) buffers modulating vaginal pH to the lower end of the physiological range, and (iii) anionic polymers that are capable of capturing viruses, such as HIV, that carry positive charges at their surface [45]. Since these agents were expected to act not only on HIV but also on other sensitive sexually transmitted pathogens, they were referred to as "microbicides". Several large-scale efficacy studies were carried out with these products during the 2000s, but none were successful. Worse, certain products were shown to increase risk of HIV transmission compared with placebo owing to their capacity to elicit local irritation and inflammation, leading to a local influx of HIV target cells [46].

Positive signs with tenofovir vaginal gel

The encouraging results emerging from the development of TDF-based oral PrEP prompted a shift of emphasis towards the development of topical prevention methods based on potent anti-HIV drugs. A first efficacy trial of a tenofovir vaginal gel used in a 24-hour window before or after sexual intercourse provided evidence of modest but statistically significant protection [47]. Neither of the two follow-up studies, one repeating the 24-hour coitally dependent usage [48], the other involving daily gel dosing [43], demonstrated efficacy, however. As with the unsuccessful TDF oral PrEP studies in women, failure in these studies was explained in terms of lack of adherence by the study participants [47, 48].

Success with dapivirine intravaginal rings

At the same time, significant efforts were being made to develop intravaginal rings that provide longer-term release of HIV inhibitors. Intravaginal rings were originally developed to enable hormonal contraceptives to be delivered locally and independently of gastrointestinal absorption over several weeks, thereby reducing systemic exposure to the drugs and facilitating adherence [49]. Work focused on rings containing dapivirine, an NNRTI with a promising safety and potency profile [50], which had been initially developed as an HIV therapeutic [51]. Two large-scale efficacy studies with dapivirine intravaginal rings showed modest but statistically significant protection from HIV infection in women in sub-Saharan Africa [52, 53]. As with the tenofovir gel studies, protection was shown to be highly dependent on the adherence level of the participants, which was considerably lower among younger women [52, 53].

Next-generation strategies that encourage user adherence are required

The success of oral TDF-based products and the dapivirine intravaginal rings has provided important new tools that are now ready to be used in the fight to contain the HIV epidemic. However, neither approach has been shown to provide consistently high levels of protection in populations located in the worst-affected regions of the world. A particular issue is the absence of a strategy shown to strongly protect women in sub-Saharan Africa, where (i) tenofovir-based PrEP trials met with several failures [42, 43], (ii) tenofovir gel failed to show efficacy [47, 48], and (iii) dapivirine rings provided only modest levels of protection [52, 53]. In each of these trials, lack of efficacy was linked to low product adherence rather than low drug potency. Some of the adherence problems with PrEP in sub-Saharan Africa may be reduced as news of its success in other regions spreads and as a consequence of political efforts to change perceptions about its use [54]. In addition, new strategies are being introduced to better incentivise adherence in younger women, for example by offering intravaginal rings that provide additional protection against other prevalent sexually transmitted diseases and/or contraceptive activity [55]. Devices providing longer-term drug release are also under development, including those that are implanted, reducing any risk of removal or loss [56].

The importance of developing rectal products

Receptive anal intercourse is the sexual behaviour that carries the highest risk of HIV transmission [57]. Practiced by many men and women around the world [58], it is probable that unprotected receptive anal intercourse is a major driver in the HIV epidemic. Whereas TDF-based oral PrEP is effective at protecting men who practice unprotected receptive anal sex [35–37], efficacy in women has not been demonstrated. Topical delivery of drugs to the vagina via either vaginal gel or intravaginal ring leads to drug accumulation in rectal tissue, but levels are typically several orders of magnitude lower than in vaginal tissue [59–61], implying that protection from rectal exposure to the virus would be significantly reduced. For this reason, efforts are being made to develop HIV prevention products for rectal or vaginal-plus-rectal use, including gels, enemas and suppositories [62]. The furthest advanced rectal product is a tenofovir gel, which provided indications of acceptable safety and tolerability in a phase II study [63].

Influence of the microbiome at mucosal surfaces

The microbiome on the sexual mucosa, which is known to impact on the HIV transmission process [64], should be taken into account during the development and evaluation of strategies for HIV prevention. In the vagina, microbiomes rich in *Lactobacillus* correlate with a lower risk of HIV acquisition [65, 66]. This is likely to be due to both (i) the capacity of *Lactobacillus* to generate a low pH environment, which is detrimental towards HIV virions, and (ii) the low level of baseline inflammation induced by *Lactobacillus* colonisation compared with other microbial populations [67]. For this reason, candidate HIV prevention agents are typically assessed during preclinical development for any potential to disrupt a protective *Lactobacillus*-rich vaginal microbiome [68].

In addition there is emerging evidence that the vaginal microbiome can influence the effectiveness of locally applied HIV prevention drugs. Follow-up analysis of the first tenofovir gel field trial showed that women with *Lactobacillus*-high microbiomes were better protected than women with *Lactobacillus*-low microbiomes. This observation was linked to higher levels of the drug measured in women with *Lactobacillus*-high microbiomes than in those with *Lactobacillus*-low microbiomes, leading to the suggestion that certain of abundant non-*Lactobacillus* microbes are capable of metabolising tenofovir, lowering its effective concentration in the tissues [69].

The rectal mucosal microbiome also shows striking heterogeneity between individuals [70], and although it has been less well studied than the vaginal mucosa, it is reasonable to assume by analogy that (i) certain microbiomes will provide better intrinsic protection from HIV acquisition then others, (ii) topically applied HIV prevention agents could influence the constitution of the rectal microbiome, and (iii) the rectal microbiome could influence the levels of rectally applied HIV prevention levels by breakdown and/or metabolism.

Integrase inhibitors for long-acting prevention

Cabotegravir is a second-generation integrase strand transfer inhibitor that has shown efficacy as a long-acting injectable PrEP agent in macaque rectal and vaginal challenge models [71–73]. In a recent phase IIa clinical study

in men, safety, tolerability and acceptability profiles of long-acting injectable cabotegravir were described as good enough to justify further evaluation of the product as an alternative to topical and orally delivered PrEP [74].

New anti-HIV drugs are needed in the pipeline

The successes achieved with dapivirine, tenofovir, tenofovir-emtricitabine and cabotegravir provide strong support for the rationale of adapting potent anti-HIV drugs for use in prevention, but some limitations remain. First, single point mutations in the reverse transcriptase gene are sufficient for circulating HIV strains to gain significant resistance to both tenofovir and tenofovir-emtricitabine [75], an alarming prospect given that these drugs are used as first-line therapeutics in infected people [76, 77]. HIV has a less rapid route to the acquisition of resistance to dapivirine, but the mutants that emerge are broadly cross-resistant to NNRTI drugs, including those commonly used in therapy [78]. The development of HIV strains resistant to integrase inhibitors has also been noted [75], although there is evidence that cabotegravir might present a higher barrier to escape [79].

Second, although tenofovir has a good safety profile in comparison with earlier anti-HIV drugs from the NRTI family, it is known to be capable of provoking renal toxicity and bone demineralisation [80], and based on evidence from similar NNRTIs and integrase inhibitors that are used in therapy [80, 81], neither dapivirine nor cabotegravir is unlikely to be completely innocuous. The safety versus efficacy balance of medicines is always a concern, but toxicity becomes an even more important issue when medicines are used prophylactically in healthy people, and any concerns about side effects will impact adherence.

It will therefore be important to introduce anti-HIV drugs into the development pipeline as the optimisation of HIV prevention strategies moves ahead. Particularly desirable attributes would be (i) no concurrent use in or development for therapy, (ii) high barriers to the development of resistant escape mutants, (iii) no generation of cross-resistance to inhibitors used in therapy, and (iv) improved efficacy versus safety profiles compared with tenofovir, emtricitabine and dapivirine. In the next part of the review we will discuss the potential use of CCR5 inhibitors in HIV prevention.

Progress

CCR5: a key player in the infection of target cells by HIV

Infection of a new host by HIV requires entry into susceptible target cells. The molecular details of the HIV entry process were established at the end of the 1990s and have been reviewed extensively [82, 83]. Entry is mediated by the HIV envelope glycoprotein complex, comprised of gp120 and gp41. The first step in the process is the engagement of CD4 on host cells by gp120, eliciting a conformational change in the envelope glycoprotein that enables gp120 to interact with a second host cell surface protein known as a coreceptor. Engagement of the coreceptor elicits a second conformational change in the envelope glycoprotein that initiates gp41-mediated virus-host cell membrane fusion.

HIV coreceptors were discovered following two key observations. First, the human chemokine proteins, MIP-1α/CCL3, MIP-1β/CCL4 and RANTES/CCL5 were identified as endogenous suppressors of HIV replication [84]. Subsequently, functional screening of a human cDNA library led to the identification of a chemokine receptor, now known as CXCR4, as an HIV coreceptor [85]. CXCR4 is not the receptor for the previously identified HIV-suppressive chemokines, but a rapid series of studies published in 1996 established that CCR5, the cognate receptor for MIP-1α/CCL3, MIP-1β/CCL4 and RANTES/CCL5, is also a functional HIV coreceptor [86–88], and that SDF-1/CXCL12, the cognate chemokine for CXCR4, also inhibits HIV infection [89, 90].

In the same year, a null allele for CCR5 known as CCR5Δ32, which encodes a truncated protein that is unable to reach the cell surface and function as an HIV coreceptor, was discovered [91, 92]. Groups of rare individuals known to have had multiple exposures to HIV-1 and not infected were genetically characterised and shown to be homozygous for CCR5Δ32 [93]. Importantly, the absence of a chemokine receptor gene in these individuals does not appear to impact on health, presumably as a consequence of the functional promiscuity of the chemokine-chemokine receptor network [94]. The dispensability of CCR5 to the host is underlined by the relatively high frequency of the allele (up to 10%), particularly in populations originating from northern and central Europe [95]. Together, these findings highlight the importance of CCR5 in HIV transmission and suggest that pharmacologically replicating the phenotype of CCR5Δ32 homozygotes would be a promising strategy for HIV prevention.

Mucosal transmission of HIV: a potential role for CCR5

It is not possible to identify and study individuals who are in the process of acquiring an HIV infection, so most of our knowledge about HIV transmission mechanisms has been acquired by use of a combination of human mucosal tissue explant cultures [96] and non-human primate models [97]. Although these models have limitations [97, 98], they provide an experimental system that is as close as currently possible to the actual transmission process in humans. Until now, the main focus of research has been on transmission of the virus following vaginal challenge [97, 99]. The key features of the transmission mechanism as it is currently understood [100–102] are summarised below and in figure 1.

Viruses cross the epithelial barrier within hours of arrival in the lumen, exploiting the single layer columnar epithelial layer of the cervix or penetrating the multilayer squamous epithelium of the vagina either at microlesions [102] or in regions where barrier permeability is locally compromised [103]. Dendritic cells, including the subset that reside in the epithelial layer (Langerhans cells), have been shown to be capable of capturing infectious virions and transferring them for infection of T cells in coculture conditions [104]. Although these cells have attributes that make them theoretically capable of playing a role in mucosal transmission, little evidence for their involvement has been found in animal and human tissue explant models so far [100–102].

The first infected target cells that can be detected in the new host are located in the subepithelial layer, giving rise to a small viral "founder population". Analysis of these infected cells reveals that they are predominantly CD4 T cells of the Th17 lineage expressing the chemokine receptor CCR6 [105], as well as CCR5. Other potential target cells are available in the subepithelial environment, such as CD4 and coreceptor-positive macrophages and dendritic cells, but it has been suggested that CCR6+ T cells are preferentially infected because they have a physiological role in epithelial repair, accumulating at the same sites of compromised epithelial barrier function that are used by HIV as portals for entry [105]. Expansion of the initial founder population is necessary for successful transmission to the new host, and this process is believed to be facilitated by the recruitment of new target cells to the focus of infection. It has been proposed that activated plasmacytoid dendritic cells, having detected the presence of local viral infection, release MIP-1α/CCL3 and MIP-1β/CCL4, which will then attract CCR5-positive T cells [106, 107]. In addition, ongoing disruption to epithelial integrity at the infection focus might elicit the recruitment of further T cells via CCR6 [105]. Within a week, infection spreads to the local lymphatic system, from where the abundance and proximity of target cells ensures that acute systemic infection is established within 2 weeks.

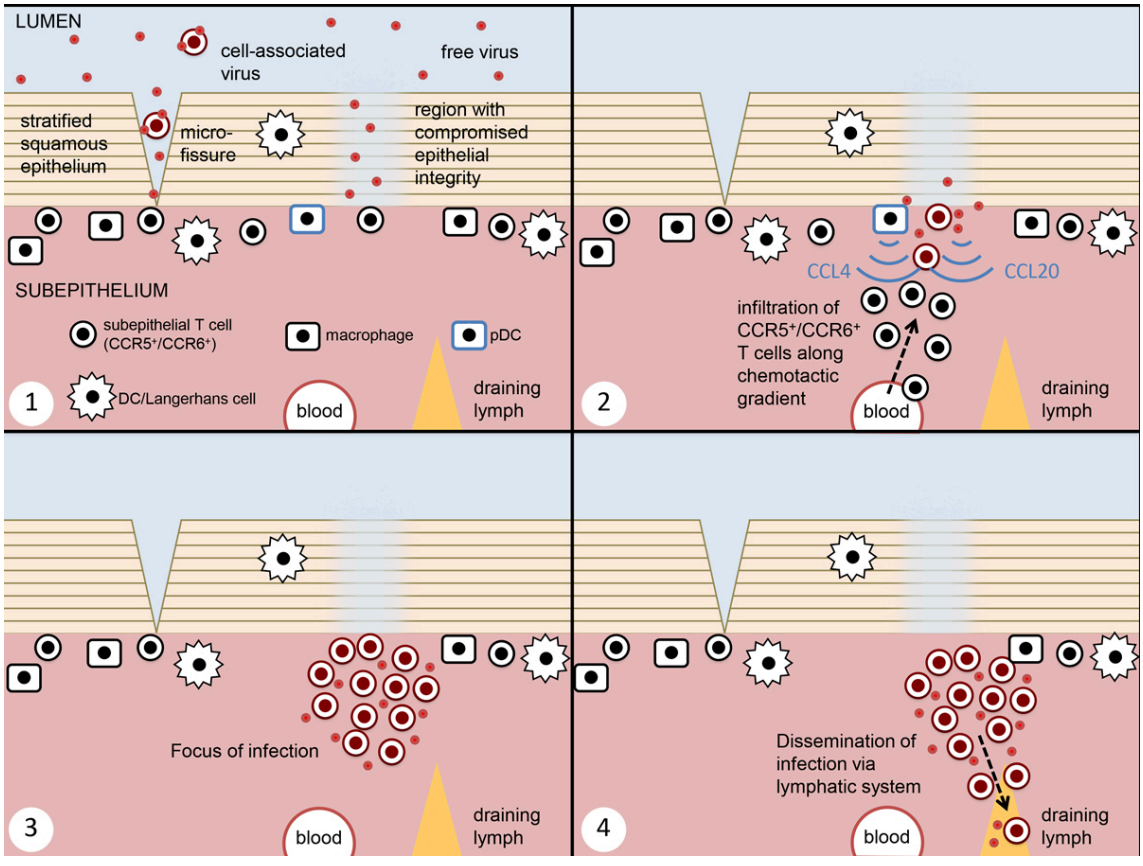
Study of transmitted viruses reveals CCR5 as a "gatekeeper" for transmission

Genetic analysis of HIV strains isolated soon after transmission in humans has revealed that, despite the presence of a genetically diverse swarm of viruses in the infected partner, in the majority of cases only a single viral species is responsible for the initiation of the founder population in the new host [101]. The successfully transmitted viruses have several distinguishing features [101]. Typically, their envelope glycoproteins have fewer glycosylation sites [108] and exhibit an increased capacity to interact directly with α4β7 integrins expressed on T cells, which may promote attachment to target cells, facilitating infection [109]. Strikingly, successfully transmitted viruses are overwhelmingly those that use CCR5, and not CXCR4, as an entry coreceptor [110, 111]. The mechanism underlying such highly stringent selection based on coreceptor usage remains unclear [112], but the observation provides both an explanation for the remarkable levels of resistance to HIV acquisition shown by individuals homozygous for the CCR5Δ32 allele, and a rationale for the development of HIV prevention approaches based on CCR5 blockade.

CCR5 blockade: small molecule inhibitors and monoclonal antibodies

The first small molecule CCR5 inhibitor to be described was TAK-779 [113]. Low oral bioavailability prevented

Figure 1: Current understanding of mucosal transmission of HIV. This figure represents infection across a squamous epithelial barrier (e.g. vagina and penile foreskin), the mechanism which has been most extensively studied. 1. Challenge arrives in the form of both cell-free and cell-associated virus, with entry at points of reduced epithelial integrity. 2. The initially infected cells are believed to be submucosal CCR5+ CD4 T cells. At sites of initial infection, both epithelial damage and innate antiviral responses lead to the release of chemokines, leading to recruitment of susceptible target cells. 3. This leads to the formation of a focus of infection, generating a population of founder virus. 4. Free and cell-associated virus from the founder population enters the lymphatic system, leading to the establishment of systemic infection.



it from being taken into clinical development, but an improved follow-up compound, cenicriviroc [114], which also has inhibitory activity against the chemokine receptor CCR2, is being taken forward for both HIV therapy [115] and non-alcoholic fatty liver disease [116]. Another small molecule CCR5 inhibitor to emerge soon after the identification of CCR5 as an HIV coreceptor was CMPD-167 [117]. Although it was not taken into development as an HIV therapeutic, it has been used extensively in preclinical models of HIV treatment and prevention. The mid-2000s saw the arrival of several other orally available small molecule CCR5 inhibitors at the end of the HIV therapy development pipeline. Aplaviroc [118] was discontinued in 2005 after evidence of hepatotoxicity emerged in phase III studies [119], vicriviroc [120] was discontinued in 2010 owing to lack of efficacy [121], but maraviroc [122] was licensed for use in HIV therapy in 2007 [123], and since then has been the sole CCR5 inhibitor in clinical use.

A large number of monoclonal antibodies specific for CCR5 have been isolated [124], some of which exhibit anti-HIV activity. Two of these have been taken into clinical development. A phase I study for HGS004 was completed in 2006 [125], but no further development has been carried out since. PRO-140 [126] is currently in phase II/III studies, with results expected during 2018 [127].

The antibody-like inhibitor eCD4-Ig consists of two domains of CD4 fused to an IgG Fc region, appended with a tyrosine-sulphated CCR5-mimetic peptide. Capable of simultaneously engaging the highly conserved CD4 and CCR5 binding sites on the HIV envelope glycoprotein, eCD4-Ig is a highly potent inhibitor of a broad range of viral isolates. Although it could in principle be developed as a protein for passive immunisation, efforts so far have focused on long-term delivery using an adeno-associated viral vector. Delivered in this format, eCD4-Ig expression levels remained detectable in the serum of macaques for at least 40 weeks, and provided complete protection from successive intravaginal viral challenges [128]. Before this promising concept can be brought into clinical development, however, it will be necessary to address several concerns related to the use of the adeno-associated viral vector system including (i) pre-existing immunity to the vectors, which limits transduction efficiency, (ii) development of an immune response against eCD4-Ig, and (iii) how to rapidly shut down expression from the vector in the event of an adverse response [129].

CCR5 blockade: nucleic acid-based approaches

Several different nucleic acid-based strategies for achieving CCR5 blockade have been developed. The first approaches involved inducing the expression of modified CCR5 ligands in the biosynthetic pathway so that they immobilise and/or degrade the receptor before it can reach the cell surface [130, 131]. Subsequently, techniques targeting CCR5 mRNA were described, including small interfering RNA [132], small hairpin RNA [133, 134], antisense RNA [135] and ribozymes [136]. Finally, DNA-modifying strategies are being developed based on zinc finger nuclease (ZFN) [137], transcription activator-like effector nuclease (TALEN) [138] and CRISPR/Cas9 [139] technologies.

CCR5 blockade: chemokine analogues

Experiments performed *in vitro* have shown that the modest anti-HIV activity of native CCR5 chemokines is due to a combination of (i) steric blockade of the HIV envelope-CCR5 interaction at the cell surface, and (ii) agonist-mediated receptor desensitisation, resulting in removal of CCR5 from the cell surface [140]. This inhibitory role is of some importance *in vivo*, since a lower probability of HIV transmission has been noted in individuals carrying a gene duplication that results in increased circulating concentrations of MIP-1α/CCL3 [141].

Chemokine analogues with potent anti-HIV activity have been developed specifically as agents for use in HIV prevention strategies. Within months of the identification of CCR5 as an HIV coreceptor, a first inhibitor, RANTES(9-68), was described [142]. This truncated version of RANTES/CCL5 did not show improved anti-HIV potency, but since CCR5 is an inflammatory chemokine receptor, its lack of signalling activity was considered advantageous. Shortly afterwards, AOP-RANTES, an analogue featuring a hydrophobic N-terminal extension with anti-HIV potency several orders of magnitude higher than that of the parent chemokine, was described [143]. In a subsequent study, further work on the N-terminal pharmacophore region of AOP-RANTES led to the identification of 50-fold more potent analogue, PSC-RANTES [144]. Like AOP-RANTES, PSC-RANTES is a CCR5 superagonist [145] whose inhibitory activity is due to its capacity to elicit profound and prolonged intracellular sequestration of CCR5 [144].

Perspectives

Several CCR5 inhibitors have been taken towards development as HIV prevention medicines. These efforts are described in the following section, and the efficacies of the drugs concerned in animal models of HIV transmission are summarised in table 1.

CCR5 inhibitors in oral PrEP

Research into the use of orally administered CCR5 inhibitors for pre-exposure prophylaxis began in the early 2000s, when the first orally available small molecule CCR5 inhibitors emerged. Oral daily dosing of CMPD-167 provided partial but statistically significant protection in a macaque vaginal challenge model [153]. Orally delivered maraviroc in a humanised mouse model provided full protection against vaginal HIV-1 challenge [151], but it was not effective at protecting macaques in a rectal challenge model, despite the accumulation of drug concentrations estimated to be 40-fold high then those required to prevent infection of macaque leucocytes *in vitro* [148].

In initial clinical studies, orally delivered maraviroc was safe and well tolerated, as expected, but did not prevent infection of mucosal explants from the subjects [154, 155], despite accumulation of high doses in the tissues concerned [155]. A recently completed phase II study of oral PrEP with maraviroc in men who have sex with men again showed that it was safe and well-tolerated, but the study was not powered to determine efficacy [156].

CCR5 inhibitors in topical PrEP: CMPD-167

At the beginning of the 2000s, a prevailing model for mucosal HIV transmission involved infection-independent uptake of virions by epithelial dendritic cells, which would then migrate to draining lymph nodes and allow the captured virus to infect T cells. In this way, the site of the first CCR5-dependent infection event would be too far from the epithelial surface to allow topically applied CCR5 inhibitors to provide any protective benefit. In line with this model, gel-formulated CMPD-167 at a concentration (1 mM) several orders of magnitude in excess of its *in vitro* potency, was capable of protecting only 2/11 animals in a macaque vaginal challenge model [147]. However, the demonstration that topically applied PSC-RANTES achieves full protection at the same concentration in the same model provided an important proof-of-concept that topical blockade of CCR5 is indeed a feasible strategy for HIV prevention [157], and when CMPD-167 was tested at a higher concentration (5 mM) in a subsequent study it protected 8/10 macaques in the vaginal challenge model [146]. Further development of CMPD-167 in the form of both gels [60] and intravaginal rings [60, 158] was initiated, but as a candidate small molecule CCR5 inhibitor for use in topical prevention it has been superseded by maraviroc, which was licensed by Pfizer to the International Partnership for Microbicides for this purpose in 2008.

CCR5 inhibitors in topical PrEP: maraviroc

Maraviroc was first tested as a vaginal gel in the macaque vaginal challenge model, where it protected 6/7 macaques when used at 6 mM concentration [150]. In a subsequent study, full protection in the model was achieved at a concentration approximately 10-fold higher [159]. Maraviroc gels have also been shown to be active in standardised human rectal and vaginal explant tissue challenge models [160]. Maraviroc has also been developed for topical prevention in the form of vaginal rings, both alone [158] or coformulated with dapivirine [161]. A phase I study of maraviroc and maraviroc-dapivirine rings indicated that whereas rings containing maraviroc are both safe and well-tolerated, they did not confer protection on explanted cervical tissue in challenge experiments, an observation that was explained in terms of the low cervical tissue levels achieved in this study [162].

CCR5 inhibitors in topical PrEP: 5P12-RANTES

Despite the breakthrough success achieved with PSC-RANTES in the macaque vaginal challenge model [157], there were concerns that the high topical doses required for full protection would prevent a chemically synthesised macromolecule such as PSC-RANTES from being affordable for use in developing countries [163]. This, together with concern over potential inflammatory activity due to its CCR5 signalling activity, prompted the search for a new generation of fully recombinant analogues (featuring only natural, coded amino acids) using a modified phage display approach [164, 165]. In this way, 5P12-RANTES, a chemokine analogue with potency [166] and efficacy [152] as high as that of PSC-RANTES, but lacking any detectable signalling activity [166], was discovered. As a fully recombinant protein, 5P12-RANTES can be produced to clinical grade using a low-cost microbial fermentation approach [167]. Many proteins would be expected to be unstable outside the cold chain, away from neutral pH and in the enzyme-rich environment around mucosal tissue, but 5P12-RANTES shows remarkable stability to temperature, vaginal pH, and incubation with samples of human semen, cervicovaginal lavage and rectal lavage [168, 169]. Finally, 5P12-RANTES presents a remarkably high barrier to the development of resistant mutants, and is active against HIV variants resistant to other CCR5 inhibitors including maraviroc [170]. Hence 5P12-RANTES represents a promising candidate for further development for use in topical HIV prevention, with current efforts focusing on a range of formulation options including gel [171, 172], vaginal ring [173] and silk fibroin disks [174].

Table 1: Preclinical efficacy testing of CCR5 inhibitors in animal models of HIV transmission.

Compound	Formulation	Dose	Animals protected	Model	Reference
CMPD-167	Vaginal gel	1 mM 5 mM	2/3 8/10	Macaque (SHIV-162P3 single challenge, 30 min after inhibitor delivery	[146]
	Vaginal gel	1 mM	2/11	Macaque (SHIV-162P4 single challenge, 15 min after inhibitor delivery)	[147]
Maraviroc	Vaginal gel	60 mM, 3.3% (w/w)	4/4	Macaque (SHIV-162P3 single challenge, 30 min after inhibitor delivery)	[60]
	Oral	44 mg/kg	1/6	Macaque (weekly challenge of SHIV-162P3, weekly exposure to inhibitor 24 hours before and 2 hours after virus exposure)	[148]
	Vaginal gel	5 mM	7/7	RAG-hu humanised mouse (HIV-1 BaL single challenge, 1 hour after inhibitor delivery)	[149]
	Vaginal gel	6 mM 2 mM 0.6 mM 0.2 mM	6/7 3/4 3/4 2/4	Macaque (SHIV-162P3 single challenge, 30 min after inhibitor delivery)	[150]
	Oral	61.5 mg/kg	6/6	RAG-hu humanised mouse (HIV-1 single challenge on day 4 of 7-day treatment)	[151]
5P12-RANTES	Vaginal solution	1 mM	5/5	Macaque (SHIV-162P3 single challenge, 30 min after inhibitor delivery)	[152]

Outlook

Will CCR5 fulfil its promise as a target for HIV prevention? Although the efficacy of a CCR5-targeting HIV inhibitor has yet to be tested clinically, studies of maraviroc in both oral PrEP [156] and intravaginal ring [162] strategies have shown it to be safe and well tolerated. It is far from clear that the investment required to take maraviroc-based products further in development will be made, however. For oral PrEP, the results obtained in mucosal explant challenge studies from study volunteers were not encouraging [154, 155], even in cases where drug levels in tissues were in the hoped-for range [155]. These results correlate with the difficulty in achieving full protection with maraviroc-based strategies in non-human primate models of mucosal challenge [148, 150], providing an indication that maraviroc might not be a sufficiently potent CCR5 inhibitor for use in HIV prevention. The International Partnership for Microbicides has suspended development of maraviroc-based topical prevention strategies [175].

If maraviroc is not taken further into clinical development for HIV prevention, what are the alternatives? Nucleic acid-based methods could in principle be used for CCR5 blockade, but the DNA editing strategies currently being developed as cell therapies in the hope of curing HIV infection would not be appropriate for use in uninfected people, and the topical strategies involving RNA interference have not progressed beyond studies in cultured cells.

Protein-based inhibitors, either monoclonal antibodies or chemokine analogues, represent a promising alternative. As a class of medicines, biologics are much less likely to cause off-target side-effects than small molecule drugs. Furthermore, for the most advanced candidate biologics in development for HIV prevention, the key issues of stability [168, 169] and costs of production [167, 176, 177] appear to have been successfully addressed.

Anti-CCR5 antibodies, in particular PRO-140, which is currently under evaluation as an HIV therapeutic, could in principle be adapted for use in either topical or systemic prevention in line with the initiative for the development of HIV envelope-specific antibodies such as 4E10, 2F5, 2G12 and VRC01 [178].

Another promising option is 5P12-RANTES, developed especially for use in HIV prevention. It has yet to be tested in humans, and significant time and resources would be required to bring it to the stage of clinical development currently occupied by maraviroc. Aside from providing indications of safety, initial clinical studies will be required to ascertain whether, as a modified host protein, 5P12-RANTES poses problems of immunogenicity. Importantly, there are indications that 5P12-RANTES might be a more potent inhibitor of mucosal HIV infection than maraviroc. Although 5P12-RANTES showed full protection in the macaque vaginal challenge model when used at a 1 mM concentration (0.8%) [152], a substantially higher concentration of maraviroc (60 mM, 3.3%) was required for full protection in the same model [159].

In conclusion, a large number of studies point to the importance of CCR5 in the transmission of HIV and its potential utility as a target for HIV prevention strategies. Maraviroc, primarily an HIV therapeutic, was the first CCR5-targeting drug to be ready for use in clinical studies of HIV prevention, but it appears not to have the all attributes required of an effective HIV prevention agent. Other molecules are available earlier in the developmental pipeline, but quite significant investments will be required to determine whether they are capable of exploiting the opportunity presented by CCR5 blockade in HIV prevention.

Acknowledgements

The authors are grateful to the Swiss National Science Foundation for support (grant 310030_163085.

Disclosure statement

O.H. is co-founder and chief scientific officer of the Mintaka Foundation for Medical Research, a non-profit organisation that is responsible for the development of 5P12-RANTES. O.H. is also the inventor on the patent covering 5P12-RANTES.

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