Reverse Transcriptase Inhibitors as Microbicides

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Abstract: The CAPRISA 004 study in South Africa has accelerated the development of vaginal and rectal microbicides containing antiretrovirals that target specific enzymes in the reproduction cycle of HIV, especially reverse transcriptase inhibitors (RTI). In this review we discuss the potential relevance of HIV-1 RTIs as microbicides, focusing in the nucleotide RTI tenofovir and six classes of nonnucleoside RTIs (including dapivirine, UC781, urea and thiourea PETTs, DABOs and a pyrimidinedione). Although tenofovir and dapivirine appear to be most advanced in clinical trials as potential microbicides, several issues remain unresolved, e.g., the importance of nonhuman primates as a "gatekeeper" for clinical trials, the emergence and spread of drug-resistant mutants, the combination of microbicides that target different phases of viral reproduction and the accessibility to microbicides in low-income countries. Thus, here we discuss the latest research on RTI as microbicides in the light of the continuing spread of the HIV pandemic from the point of view of medicinal chemistry, virological, and pharmaceutical studies.

Keywords: Microbicide, HIV, reverse transcriptase, NtRTI, NNRTI, NRTI, gel, intravaginal ring.

INTRODUCTION

The year 2010 has been a turning point in the microbicide field as a result of the announcement of the positive outcome from the prevention trial with tenofovir intravaginal gel by the CAPRISA (Center for AIDS Programme in South Africa) 004 study [1].

Earlier reviews of RTI-microbicides have pointed to the challenges that arise with their development. These include (1) the lack of strong and consistent evidence of efficacy in nonhuman primates, (2) the risk of selecting and promoting the spread of drug-resistant viruses when applied clinically, (3) the choice of a suitable combination microbicide, (4) acceptability and (5) affordability [2-4].

Preclinical studies on macaques have been promoted for demonstrating efficacy, adequacy of treatment regimens, emergence of drug-resistant mutants and immune response to candidate microbicides [5, 6]. However, the robustness and reproducibility of macaque studies leave room for improvement.

Formulation plays an important role in the development of RTI-microbicides. Ideally, high concentrations need to be achieved in aqueous vaginal and rectal environments, while at the same time the agents must be able to permeate lipid membranes [7]. Clearly, it is a difficult challenge to find optimal formulations for combinations of microbicides. This is one of the main objectives of CHAARM (Combined Highly Active Anti-Retroviral Microbicides), a research consortium sponsored by the 7th Framework Programme (FP7) of the European Commission [8].

In this review, the discussion of RTI-microbicides will be limited to antiviral agents that are to be delivered intravaginally or rectally in the form of a gel, ring or film. HIV refers to HIV type 1 (HIV-1), unless stated otherwise.

1. Nucleotide RTIs (NtRTIs)

Similar to nucleoside RTIs (NRTIs), NtRTIs are polymerization chain terminators, acting at the polymerization site of RT (Fig. **1**) [9]. Unlike NRTIs, an NtRTI requires only two phosphorylation steps by AMP kinase in order to be turned into the active drug, thus avoiding the first rate-limiting phosphorylation [10].

1.1. Tenofovir

Tenofovir (TFV, PMPA) is an acyclic phosphonate derivative of adenine (Fig. **2**). Its invention and development has been the result of a long-standing collaboration between Erik De Clercq (Rega Institute for Medical Research of the Catholic University of Leuven, Belgium), Anthonin Holý (Czechoslovak Academy of Sciences, Czech Republic) and James Martin (Gilead Sciences, Foster City, CA). Initially, emphasis was on coitally independent oral pre- and post-exposure prophylaxis (PrEP and PEP) rather than on the potential use of TFV as a microbicide [11].

1.1.1. Cellular and Explants Tests

Synergy has been observed in combinations of TFV, dapivirine and UC781 in cellular tests and colorectal explants. None of these compounds or their combinations

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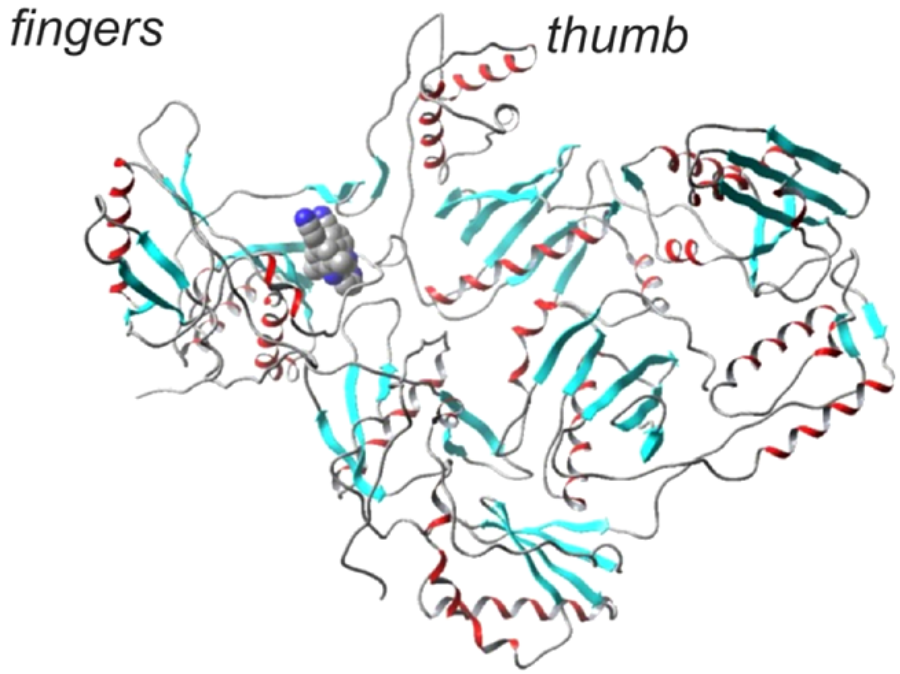

Fig. (1). Model of HIV- RT [9]. The polymerization site is formed by the fingers and thumb domains. A close analog of dapivirine (rilpivirine) is shown within the NNRTI binding site. Copyright (2008) National Academy of Sciences, USA.

affected the viability of colorectal tissue [12]. TFV has been found to possess a long intracellular half-life, exceeding 60 hrs [13].

1.1.2. Animal Safety, Pharmacokinetic and Efficacy Tests

Macaques inoculated with SIV (simian immunodeficiency virus) showed no viral replication after treatment for 28 days by subcutaneous injection of TFV [14]. Remarkably, high-dosed rectally applied tenofovir gel protected 6/9 macaques from SIV infection [15], whereas TFV alone or in combination with emtricitabine was reported to fully protect macaques from SHIV (simian-human immunodeficiency virus) infection. The discrepancy was explained by macaque models with different stringencies [16]. In the humanized BLT (bone marrow, liver, thymus) mice model [17], the combination of TFV with emtricitabine yielded only partial protection against infection by HIV [18]. These observations illustrate the present lack of robustness and consistency of animal microbicide studies on TFV.

1.1.3 Phase I/II Trials

Tenofovir was found to be safe and well-tolerated in a study on HIV-negative women with tenofovir vaginal gel applied during 24 weeks [HPTN 059]. Repeated application of TFV intravaginal gel was well-tolerated, produced low plasma levels and did not select for drug-resistant mutations [19]. A pharmacokinetic study with repeated application of TFV gel in seronegative women showed that plasma levels of TFV were low, while vaginal fluid and tissue concentrations were high [20]. The anti-HIV activity of CVL (cervico-vaginal lavages) has been proposed as a biomarker for pharmacokinetics and immune response of TFV and as a surrogate test for safety and efficacy of vaginal microbicides [21].

A first ongoing study [MTN001] compares adherence and pharmacokinetics of oral and vaginal applications of TFV in seronegative women. The second ongoing VOICE safety and pharmacokinetics study [MTN003] compares TFV intravaginal gel with oral TFV disoproxil fumarate with and without emtricitabine [22].

1.1.4. Phase III Trial

The double-blind placebo controlled CAPRISA 004 study of tenofovir intravaginal gel in seronegative women showed a significant 39% reduction of HIV-transmission over placebo ($p = 0.019$). No serious drug-related adverse effects were observed [23]. The CAPRISA 004 trial has been a landmark and turning point in the history of microbicides. It has leapfrogged the projected time line for their development [24]. Apprehension against the initial trial proposal was inspired by fear for the selection and spread of drug-resistant mutant strains of HIV [2] and by previous failures of large-scale microbicide trials with non-specific agents [25]. The study has also been controversial because of a less than optimal dosing regimen, which was 12 hrs before and 12 hrs after sexual contact [26].

Several clinical studies have been proposed as a follow-up to CAPRISA 004. These include a multicentric replication of CAPRISA 004 (FACTS 001), a clinical study with a simplified dosing regimen of TFV (MDP 302) and a feasibility and effectiveness study of TFV gel in a realistic clinical setting (CAPRISA 008) [27].

2. Nonnucleoside RTIs (NNRTIs)

Unlike the polymerization chain terminators (NtRTIs and NRTIs), NNRTIs bind to an allosteric binding pocket which is situated immediately below the polymerization site of RT

(Fig. **1**). The NNRTIs discussed here are tight-binding ligands as they allow a typical butterfly conformation when bound to RT, which is capable of making extensive and strong interactions with the critical amino acid residues of the binding site [28]. They generally have nanomolar activities on wild type as well as on single and multiple mutated viral strains. NNRTIs are lipophilic compounds allowing cell permeation and providing for a long intracellular residence time, but are also mostly poorly soluble in aqueous media.

NNRTIs have been found to be generally virucidal, to have high activity on cell-free and cell-associated viruses and to possess high selectivity in cellular tests, in cervical and colorectal explants and in dual chamber experiments [29-34]. They also possess a memory effect against mucosal transmission of HIV which is attributed to their long intracellular residence time [35].

2.1. Dapivirine

Dapivirine (DPV, TMC120, R147681) is the prototype of the DAPY (diarylpyrimidine) class of NNRTIs (Fig. **2**). It was invented at Janssen Pharmaceutica and Tibotec (Beerse and Mechelen, Belgium) as the result of prolonged research which originated from a collaboration between Paul Janssen (founder of Janssen Pharmaceutica) and Erik De Clercq [10]. DPV was originally developed for therapy of HIV-patients and has successfully completed a phase II trial in which it was found be a potent and safe antiviral agent [36]. It was not developed further by Tibotec because etravirine (Intelence^{TM}) appeared to be a better alternative. Consequently, DPV was donated by Johnson & Johnson (the parent company of Tibotec) to IPM (International Partnership for Microbicides) for development as a microbicide [37, 38].

DPV has good oral bioavailability in humans [39] contrary to what has been reported repeatedly in the literature [30, 40-42]. The plasma half-time of DPV is about 70 hrs [43]. DPV spontaneously forms aggregates under conditions that prevail in parts of the intestine (Peyer's patches), where the particles are taken up and delivered to the lymphatic system [44, 45]. When applied intravaginally, there is evidence that DPV is absorbed by the outer mucosal

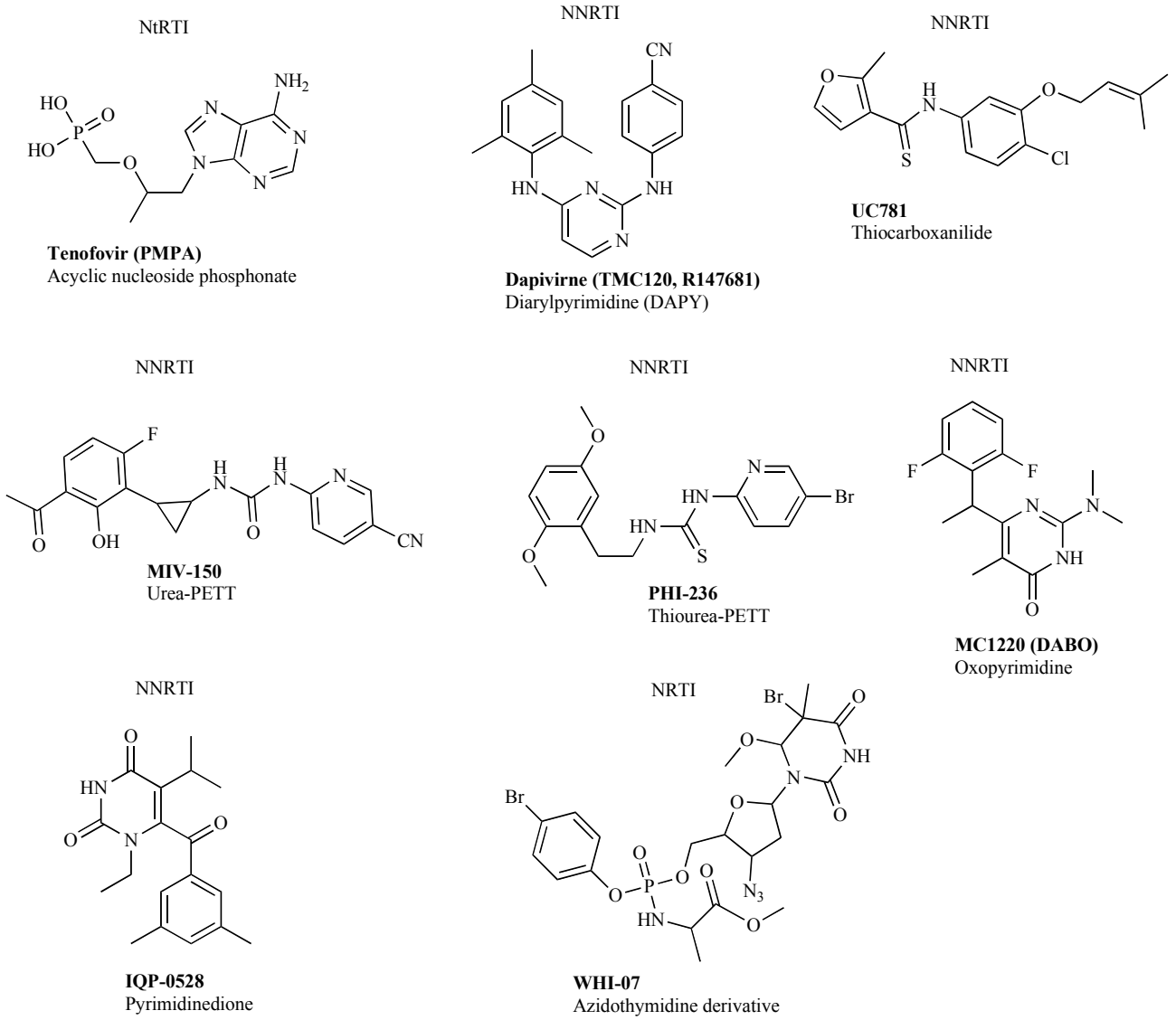

Fig. (2). Chemical structures of RTIs which have been proposed as microbicides.

layers, while plasma concentrations remain low [46]. Long-term constant release of DPV has been obtained from silicon reservoir-type and from polyether urethane matrix-type IVRs (intravaginal rings) under sink conditions [47, 48].

NNRTIs are capable of permeating cell-free HIV and inhibit HIV-NERT (natural endogenous RT) activity [49, 50]. Analogs of DPV are also potent inhibitors of HIV-NERT (Personal communication to PL by A. Tanuri[1]). Thus, these agents might inactivate the virus, even before it has penetrated into cells. In accordance with this assumption, DPV has been shown to inhibit plate-immobilized cell-free virus [51].

2.1.1. Cellular Tests

Overall, dapivirine has single-digit nanomolar activity against reproduction of HIV in cellular tests. It has been found to be a potent inhibitor of cell-free and cell-associated HIV, co-cultured in MO-DC (monocyte-derived dendritic) cells and CD4+ T cells, even if the exposure to the drug is limited to the first day of a 2-weeks culture period [32, 52, 53]. DPV also potently blocked HIV-infected cell cultures in a dual chamber model of transepithelial transmission, where the drug together with cell associated virus was added on top of a tight epithelial cell layer, whereas the target cells (MO-DC and T cell co-culture) were present in the lower chamber [32]. Synergy between DPV and TFV has been reported against a viral HIV-strain carrying the Y181C mutation, which is associated with NNRTI-resistance [54].

2.1.2. Explants Tests

A DPV gel formulation inhibited HIV in cervical explants and produced a strong memory effect which lasted for several days. There was no effect on viability of epithelial cells, cervical tissue and expression of cytokines [55]. In cervical explants DPV inhibited a panel of HIV-subtypes after exposure during 2 to 24 hrs. It was also found to be active against NNRTI-resistant viruses and clinical isolates. No cytotoxicity was observed [56]. DPV also inhibited HIV-replication in colorectal explants [57].

2.1.3 Animal Efficacy Pharmacokinetics and Safety Tests

Evidence of efficacy and safety of DPV gel was obtained in hu-SCID (humanized severe combined immunodeficient) mice. Systemic absorption was low and no vaginal trauma was observed [58]. Repeated applications of DPV gel formulations to macaques and rabbits provided evidence that DPV is absorbed in cervical tissues at concentrations that are higher than required for 99% inhibition of HIV in cervical explants tests. Concentrations in plasma and lymphatic nodes remained low [46].

2.1.4. Phase I/II Trials

IPM has planned, is completing or has completed up to now 14 I/II studies on DPV as a microbicide [38]. In a randomized double-blind placebo-controlled phase I study on HIV-positive women, a DPV gel formulation was found to be well-tolerated when applied twice daily for 1 week. Plasma levels were 1,000 times lower than trough plasma levels in a 7-day phase II oral monotherapy study of DPV [42, 59]. Phase I studies in seronegative women with a silicon reservoir-type IVR loaded with DPV and applied during 1 week showed that intravaginal concentrations of DPV were more than 1,000 times higher than the median effective concentration in cellular tests for inhibition of HIV (EC_{50}). Plasma concentrations were low (< 50pg/ml). The use of the IVR was found to be safe and well-tolerated [60].

A comparison of matrix- and reservoir-type IVRs loaded with DPV and applied during 1 month by HIV-negative women showed that intravaginal concentrations of DPV were 10,000 times higher than the EC_{50}. Intravaginal and plasma concentrations were about 10 times higher with the matrix-type IVR than with the reservoir-type IVR. Plasma concentrations were generally low (< 2ng/ml). No serious drug-related adverse events were observed [61].

A pharmacokinetics and safety study of DPV gel formulations in seronegative women showed that intravaginal concentrations were 100,000 times larger than the EC_{50}. The intravaginal half-life time of DPV was 16 hrs. The formulations were found to be safe and well-tolerated [43].

IPM has also planned a phase I combination study of DPV with maraviroc, an approved CCR5-entry inhibitor of HIV [38].

2.1.5. Phase III Trial

IPM has planned a large-scale study of DPV formulated in an IVR, with reported starting date of 2011 [38]. To our knowledge, no details on the set-up or precise starting date have been unveiled.

2.2. UC781

UC781 originated from Uniroyal Chemical (Guelph, Ontario, Canada) and has been transferred for development as an HIV-microbicide to Biosyn and CONRAD (Contraceptive Research and Development). The compound belongs to the class of thiocarboxanilides (Fig. **2**). Similar to dapivirine, it binds tightly to the allosteric binding site of HIV-RT [62] from which it dissociates slowly [63].

UC781 has been identified as an NNRTI with a broad spectrum of activities against wild type and mutated strains of HIV [64-67]. The compound is highly lipophilic. Nevertheless it was found to possess oral bioavailability in mice [68]. This may be explained by the spontaneous formation of microsuspensions which facilitate absorption by the gastro-intestinal tract [69]. Aqueous solubility of UC781 can be greatly increased when formulated with cyclodextrin [70]. The development of UC781 for oral therapy of HIV-infected patients was abandoned, apparently because of low human oral bioavailability [71].

2.2.1. Cellular Tests

On average, UC781 has double-digit nanomolar activity against reproduction of HIV in cellular tests. UC781 is active against cell-free and cell-associated HIV [72], inhibits reproduction of HIV under conditions that mimic the intravaginal environment [67] and blocks HIV in co-cultures with MO-DC and CD4+ T cells [32, 52] It inhibits immobilized cell-free virus [51] and partially blocks infection by HIV-cultures in a dual chamber model [34]. When tested against a panel of NNRTI-resistant cell-free and cell-associated viruses, the activity of UC781 decreased between 10- and 100-fold [73]. In a classical dose escalating

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in vitro setting, resistance to UC781 was more rapidly induced than to dapivirine [74].

In one study UC781 was found to act synergistically with AZT (azidothymidine) [68], while no synergy between UC781 and AZT was observed in another [75]. This illustrates the difficulty of obtaining reproducible measures of synergy between potential microbicides across different laboratories. Synergy has also been reported between UC781 and CAP (cellulose acetate benzenedicarboxylate), an entry-blocker targeting surface proteins of HIV [76].

2.2.2. Explants Tests

UC781 was found to be safe and provided prolonged protection against HIV in cervical explants tests [55, 77, 78]. A gel formulation of UC781 blocked HIV and prevented dissemination by migratory cells in a human cervical explant model [71]. UC781 was also found to be effective in a colorectal explant model [57].

2.2.3. Animal Efficacy, Pharmacokinetics and Safety Tests

Concentrations obtained in rabbits by matrix-type IVR ring segments loaded with UC781 were 100 times larger than the EC_{50} [79]. Micronized UC781 vaginal gel formulations produced greater release rates in rabbits than non-micronized ones. Vaginal concentrations were 1,000 times higher than the EC_{50}. Plasma levels were low (< 2 ng/ml) [80]. Water-based formulations of UC781 were tested vaginally and rectally in macaques. Concentrations of UC781 in cervicovaginal lavages were 10,000 times higher than the EC_{50}. No significant effects were observed on vaginal tissue, vaginal flora and cytokines. The compound was undetectable in plasma [81].

2.2.4. Phase I/II Trials

A safety study in seronegative women with UC781 gel applied once-daily during 6 days revealed only slight and transient irritation. Plasma levels were mostly undetectable [82].

2.3. Urea PETTs

2.3.1. MIV-150

MIV-150 originated from Medivir (Huddinge, Sweden). The product has not been tested for systemic use, but was transferred to the Population Council for development as a microbicide [83]. PETT is the abbreviated chemical name for phenylethylthiazolylthiourea. Thiourea has been replaced by urea in the Medivir microbicide analogs, where it is connected to the left wing substituted phenyl by means of a cyclopropyl moiety (Fig. **2**). The N-atom in the right wing pyridine of MIV-150 may form an intramolecular H-bridge with the distant NH of the urea group, which can force the molecule into the butterfly conformation of a tight-binding NNRTI.

MIV-150 has sub-nanomolar activity against cell-associated and cell-free viruses and possesses a favorable resistance profile against single and double mutated strains of HIV, as well as against a broad panel of clinical isolates [84].

In vitro, the combination (PC817) of MIV-150 and carrageenan gel (Carraguard^{TM}) was found to have an additive effect [85]. In a phase III study, carrageenan gel by itself did not significantly reduce HIV infection in women, but it was found to be safe and acceptable [86]. The application of a MIV-150/carrageenan rectal gel combination (PC817) protected 50 or 100% of macaques, depending on the challenge dose of SHIV. MIV-150 was not detected systemically [87]. In another macaque study, however, vaginally applied MIV-150 presented no additional benefit when combined with carrageenan gel, which by itself protected 75% of animals infected by SHIV. This was explained by a dominant barrier effect of carrageenan [88].

A repeated vaginal formulation of MIV-150, zinc acetate and carrageenan gel was reported to fully protect macaques against SHIV infection up to 24 hrs after the last application [89**]**.

2.3.2. MIV-160

MIV-160 is a close analog of MIV-150. The compound also possesses an N-atom in the right wing pyridine which can make a conformationally favorable intramolecular H-bridge [90]. MIV-160 has potent *in vitro* activity against wild type and mutated HIV strains and is presently in preclinical development as a vaginal HIV-microbicide. The compound has been licensed to Mefuvir Beijing [91].

2.3.3. MIV-170

MIV-170 is another analog of Medivir's MIV-150. Biosensor measurements showed that MIV-170 has a rapid association rate and slow dissociation rate from the allosteric HIV-RT binding site. It has potent anti-HIV activity on wild type and drug-resistant viruses. It is rapidly metabolized and was therefore also deemed less suitable for oral therapy of HIV [92]. MIV-170 is presently in preclinical development as an HIV-microbicide [74].

2.4. Thiourea PETTs

The thiourea PETTs are developed at the Parker Hughes Institute and Paradigm Pharmaceuticals (St. Paul, MN). These compounds are close analogs of the NNRTI trovirdine in which the left wing has been replaced by dimethoxyphenyl (PHI-236), cyclohexene (PHI-346) or thiophene (PHI-443). Similar to MIV-150 and MIV-160, the N-atom of the right wing pyridine of these thiourea PETTS is capable of forming a conformationally favorable intramolecular H-bridge [30].

2.4.1. PHI-236

PHI-236 (Fig. **2**) has high activity and selectivity on wild type HIV (< 1nM), on multi-drug resistant strains and on non-subtype B clinical isolates [30]. The compound is highly lipophilic and has been reported to have low oral bioavailability [93]. It significantly protected hu-SCID mice from infection by HIV. As PHI-236 is non-spermicidal it has been proposed for pretreatment of semen in artificial insemination [29].

2.4.2. PHI-346

PHI-346 is a highly lipophilic NNRTI with potent activity against multidrug-resistant HIV in hu-SCID mice. It also has high selectivity in female tract epithelial cells [30]. The compound has dual functions with both anti-HIV and sperm-immobilizing activities [94, 95].

2.4.3. PHI-443

PHI-443 is a highly potent NNRTI against a broad spectrum of HIV-strains. A PHI-443 gel formulation lacked toxicity in rabbits and pigs. It completely protected hu-SCID mice against vaginal transmission of wild type virus and a drug-resistant isolate. In rabbits, PHI-443 is not spermicidal and repeated application was safe and devoid of systemic absorption [30, 96].

A gel combination of PHI-443 with stampidine (a prodrug of the NRTI stavudine) was found to be safe in a rabbit irritation test [97]. The combination is not spermicidal in rodent and non-rodent tests, and was shown to be highly potent against non-subtype B strains and against clinical isolates with resistance against NRTIs and NNRTIs [98].

2.5. Oxopyrimidines

2.5.1. MC1220 (DABO)

MC1220 (DABO) is an oxopyrimidine derivative (Fig. **2**). It is a tight-binding HIV-NNRTI [99] and was extensively studied by the 6th European Framework Programme SHIVA (Selection and development of microbicides for mucosal use to prevent sexual HIV-transmission/acquisition). The compound has a strong *in vitro* memory effect. It had no effects on vaginal mucosal tissue in a toxicity study in rabbits. But, slight vaginal irritation was observed in macaques [35] Similar findings in rabbits were reported in another study. Plasma levels were low (4.5 to 30 nM) in this study [100]. An efficacy study in macaques with a vaginal liposomal gel formulation of MC1220 protected 3/5 of the animals from infection by SHIV [101].

The authors are not aware of reports on phase I studies on MC1220.

2.5.2. S-DABO

In S-DABO the dimethylamino substituent in DABO has been replaced by a thioether. S-DABO has potent *in vitro* activity on HIV and is also spermicidal. It has no toxicity on human cervical explants [102] and has been proposed as a candidate HIV-microbicide [30, 103].

2.6. Pyrimidinedione

2.6.1. IQP-0528

IQP-0528 is a pyrimidinedione derivative (Fig. **2**) developed by ImQuest Biosciences (Frederick, MD), IPM and CONRAD as a dual-acting HIV-microbicide with activities against RT and viral entry. Presumably because of this dual action mechanism and in contrast to other NNRTIs, IQP-0528 has high activity and selectivity against both HIV-1 and HIV-2. It is also active against clinical isolates and several NNRTI-resistant strains [104-108]. The sterilizing concentration of IQP-0528 was determined to be more than 2,000 times greater than the EC_{50} [109].

Release of IQP-0528 from a matrix-type IVR was constant and stable [107]. A formulation as a nontoxic polymeric film (biofilm) rapidly released the active compound [110]. A gel formulation with IQP-0528 had nanomolar activity *in vitro* and completely protected cervical explants from infection by HIV. No effect on cell viability or immune response was observed [108]. Prolonged application of a polyurethane IVR loaded with IQP-0528 in macaques produced intravaginal concentrations which were 10,000 times higher than the EC_{50}. No changes were observed in systemic and mucosal cytokines. Plasma levels were undetectable [111].

3. Nucleoside RTIs (NRTIs)

3.1. WHI-07

WHI-07 (DDE46) is a derivative of AZT (Fig. **2**) which was rationally designed at the Parker Hughes Institute [112]. Several preclinical studies have been carried out on WHI-07. These include (1) vaginal and rectal efficacy studies in cats with FIV (feline immunodeficiency virus), (2) an efficacy study in monkeys, (3) a contraceptive study in rabbits, (4) reproductive and developmental toxicity studies in mice, rabbits, cats and monkeys and (5) cytotoxicity, mutagenicity and genotoxicity tests in human and yeast cells. The overall conclusion of these studies is that WHI-07 is an effective and safe dual function microbicide and spermicide [113-115].

A 2-year toxicity study with vaginal applications of WHI-07 in mice did not produce increased carcinogenicity [114]. Vaginal coformulations of WHI-07 with the antileucocytic compound VDDTC (vanadocene dithiocarbamate) in rabbits did not produce inflammation or changes in cytokines. VDDTC may block the transfer of infected leucocytes among sexual partners [116].

CONCLUSION

It is now broadly admitted that antiretroviral agents targeting specific enzyme functions of the viral replication cycle of HIV are potential microbicides. The CAPRISA 004 study has shortened the development time for bringing an effective, safe and affordable microbicide to the general population by several years. As discussed here, the NtRTI tenofovir and the NNRTI dapivirine have progressed farthest in the development as potential RTI-microbicides. However, the most urgent question in the RTI-microbicide field is to decide which other antiretroviral should be combined with tenofovir or dapivirine and how to formulate the combination for optimal efficacy, safety and affordability. It also appears that several other NNRTIs are progressing to the status of microbicide candidate, although their characteristics may be too similar to provide a real added value or alternative to tenofovir or dapivirine.

In view of the typical lengthy process, both preclinical and clinical phases, to develop a microbicide, it is time to reflect on the next generation of microbicides. Compounds that target other stages of the HIV-replication cycle, such as entry and integrase inhibitors, may also become important microbicide candidates. They may form optimal combinations with the RTIs that are presently in advanced clinical stages for development as a microbicide.

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CONFLICT OF INTEREST

Paul Lewi and Jan Heeres are co-inventors of the DAPY class of compounds, but have no financial interest in it.

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