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CCR5 Antagonists in the Treatment of Treatment-experienced Patients Infected with CCR5 Tropic HIV-1

Thore Lorenzen, Albrecht Stoehr, Irene Walther, Andreas Plettenberg

ifi – Institute of interdisciplinary medicine, Hamburg, Germany

Abstract
CCR5 antagonists are a newly developed class of antiretroviral drugs which inhibit viral entry into the host cell by binding to the predominant HIV coreceptor. Data on the use of these new drugs in treatment-experienced HIV patients are emerging. Clinical trials on maraviroc and vicriviroc in pretreated patients recruited more than 1300 individuals. Interim results of these studies indicate that pretreated patients infected with CCR5-tropic viruses benefit from their use in optimized combination regimens. Maraviroc reduces the HIV-1 viral load in patients with previous triple-class failure by 1.96 $\log_{10}$ copies/ml versus 0.99 $\log_{10}$ copies/ml in placebo; vicriviroc shows potency by dose depending viral decrease of 1.51 – 1.68 $\log_{10}$ copies/ml compared to 0.29 $\log_{10}$ in placebo. As expected, CCR5 antagonists do not reduce viral load in patients harbouring CXCR4-tropic or dual/mixed tropic viruses. Nevertheless, since a considerable percentage of late-stage HIV patients still bear CCR5-tropic viruses, the use of CCR5 antagonists appears promising in properly selected treatment-experienced patients.

Key words: CCR5 inhibitor, HIV infection, treatment-experienced patients, tropism

Introduction

Within the last decade, antiretroviral therapy for infection with human immunodeficiency virus Type 1 (HIV-1) has made rapid progress predominantly through the development and approval of new reverse transcriptase and protease inhibitors. In addition, the concept of entry inhibition entered routine therapy in 2003, when enfuvirtide, the first HIV fusion inhibitor, was licensed. However, resistance to drugs of these classes may emerge on treatment, compromising therapeutic efficacy. Patients may carry viruses with loss of susceptibility to agents from all currently available antiretroviral classes. Drugs exploiting novel mechanisms of action are obviously needed to expand the therapeutic options for treatment-experienced patients. Therefore, the advent of CCR5 antagonists, agents blocking the interaction of HIV with its predominantly used coreceptor on the surface of CD4 cells, raises great hope in the HIV/AIDS community. Current clinical studies show promising virological activity of agents from this new class, although the optimal timing of their use in the continuum of antiretroviral therapy remains to be determined.

Epidemiological studies revealed that HIV-1 strains in antiretroviral therapy-naïve patients predominantly exhibit CCR5 tropism (R5 viral variants) [1-3]: More than 80% of treatment-naive HIV-1 infected individuals carry R5 viruses. In the treatment-experienced population, R5 viruses still account for 48–62% of isolates; dual or mixed-tropic viruses capable of using both CCR5 and/or CXCR4 coreceptors (R5/X4 variants) are found in 34–50% of these patients, while viruses that exclusively use the CXCR4 coreceptor for cell entry (X4 variants) are seen in only 2–4% of the pretreated population [4-6].

At first glance, these observations may favour the use of CCR5 antagonists in treatment-naive patients or at least in early stages of antiretroviral therapy. However, as mentioned above, a large percentage of treatment-experienced patients harbour CCR5-using viruses and may thus benefit from the inclusion of a CCR5 antagonist in an antiretroviral combination regimen.

Clinical trials on the use of CCR5 antagonists in treatment-experienced patients are ongoing. Table 1 shows an overview of studies with published data in pretreated patients. Current substances in clinical development are maraviroc, vicriviroc and INCB9472. Additionally, another small-molecule CCR5 antagonist, TAK-652, is in preclinical phase.

Maraviroc

The most advanced candidate, maraviroc (MVC) manufactured by Pfizer Inc., has recently been licensed.

Two randomized placebo-controlled phase 2a dose-finding studies (A4001007 and A4001015) investigated the antiviral efficacy of MVC in short-term monotherapy of patients who where either treatment-naive or off treatment for >8 weeks. Inclusion criteria were of viral load >5,000 HIV-1 RNA copies/ml, CD4 count >250 cells/mm^3 plus confirmed CCR5-tropism; 82 patients were randomized. No significant difference between treatment-naive or pretreated patients was observed. One accidentally enrolled patient infected with a R5/X4 virus experienced only a marginal change of viral load at day 11 (–0.33 $\log_{10}$ copies/ml) [7].

Table 1. Overview of studies on CCR5 antagonists in treatment-experienced patients.

Study		**A4001027 (Motivate-1)**	**A4001028 (Motivate-2)**	**A4001029**	**ACTG 5211**	**GW873140**
Substance		**Maraviroc (MVC)**	**Maraviroc (MVC)**	**Maraviroc (MVC)**	**Vicriviroc (VVC)**	**Aplaviroc (APL)**
Viral tropism		CCR5	CCR5	dual/mixed-tropic, CXCR4-tropic	CCR5	CCR5
Study Phase		Phase 3	Phase 3	Phase 2	Phase 2	Phase 2
No. of patients randomized		601	475	190	118	40
Treatment arms		Placebo + OBT MVC QD + OBT MVC BID + OBT	Placebo + OBT MVC QD + OBT MVC BID + OBT	Placebo + OBT MVC QD + OBT MVC BID + OBT	Placebo + OBT* VVC 5 mg QD + OBT* VVC 10 mg QD + OBT* VVC 15 mg QD + OBT*	Placebo APL 200 mg QD APL 200 mg BID APL 400 mg QD APL 600 mg QD
Inclusion Criteria		triple-class-experienced and/or documented resistance to 3 antiretroviral drug classes HIV-1 RNA ≥ 5000 copies/ml	triple-class-experienced and/or documented resistance to 3 antiretroviral drug classes HIV-1 RNA ≥ 5000 copies/ml	triple-class-experienced and/or documented resistance to 2 antiretroviral drug classes HIV-1 RNA ≥ 5000 copies/ml	>1 virological failures current ritonavir-containing regimen HIV-1 RNA ≥ 5000 copies/ml CD4 cell counts ≥ 50 cells/mm^3	Naïve or treatment-experienced and 90days off treatment CD4 cell nadir > 200 cells/µl HIV-1 RNA >5000 copies/ml
Baseline characteristics	HIV-1 RNA level, mean, copies/ml	4.84/4.85/4.86 log_{10}	4.89/4.87/4.84 log_{10}	5.01/5.03/5.10 log_{10}	4.56 log_{10} (Median)	4.28/4.26/4.42/4.46/4.37 log_{10} (Median)
	CD4 cell count, median	163.3/167.5/150.0 cells/µl	174.3/174.3/182.0 cells/µl	41.4/39.5/43.1 cells/µl	161/155/118/128 cells/µl	297/344/299/372/404 cells/µl
Virological and immunological response	HIV-1 RNA: change from baseline, mean, log_{10} copies/ml	Placebo: -1.03 MVC QD: -1.82 MVC BID: -1.95	Placebo: -0.93 MVC QD: -1.95 MVC BID: -1.97	Placebo: -0.97 MVC QD: -0.91 MVC BID: -1.20	Placebo: -0.29 5 mg VVC: -1.51 10 mg VVC: -1.86 15 mg VVC: -1.68	Placebo: -0.12 200 mg QD: -0.46 200 mg BID: -1.23 400 mg QD: -1.03 600 mg QD: -1.66
	HIV-1 RNA: < 400 copies/ml	Placebo: 31.4 % MVC QD: 54.7 % MVC BID: 60.4 %	Placebo: 23.1 % MVC QD: 55.5 % MVC BID: 61.3 %	Placebo: 24.1 % MVC QD: 24.6 % MVC BID: 30.8 %	Placebo: 11 % 5 mg VVC: 43 % 10 mg VVC: 53 % 15 mg VVC: 47 %	
	HIV-1 RNA: < 50 copies/ml	Placebo: 24.6 % MVC QD: 42.2 % MVC BID: 48.5 %	Placebo: 20.9 % MVC QD: 45.6 % MVC BID: 40.8 %	Placebo: 15.5 % MVC QD: 21.1 % MVC BID: 26.9 %	Placebo: 7 % 5 mg VVC: 26 % 10 mg VVC: 40 % 15 mg VVC: 27 %	
	CD4 cell count change from baseline, mean, cells/mm^3	Placebo: +52 MVC QD: +107 MVC BID: +11	Placebo: +64 MVC QD: +112 MVC BID: +102	Placebo: +36 MVC QD: +60 MVC BID: +62	Placebo: -9 5 mg VVC: +84 10 mg VVC: +142 15 mg VVC: +142	

* OBT in ACTG had to contain Ritonavir

Two randomized trials (A4001027 and A4001028, or MOTIVATE-1 and -2) explored MVC in treatment-experienced HIV-infected patients harbouring CCR5-tropic strains. Twenty-four week interim data of both studies were presented at the 2007 Conference on Retroviruses and Opportunistic Infections (CROI) [8,9]. Meanwhile, these trials are completed and final data are expected to be presented at one of the infectious disease conferences later in 2007.

Both trials were double-blind placebo-controlled multicenter phase 2b/3 studies investigating the efficacy and safety of MVC plus optimized background therapy (OBT) vs. placebo plus OBT in viraemic patients carrying CCR5-tropic virus. MOTIVATE-1 was conducted in the US and Canada, while the identically-designed MOTIVATE-2 trial enrolled patients in Europe, Australia and North America. The primary endpoint of both studies was the mean change in HIV-1 RNA from baseline at week 48.

According to the published data of the preplanned 24-weeks interim analyses [8,9], patients included in these studies were triple-class-experienced. The combined population of both trials had a median of 6 resistance mutations (range 0-13) relevant to nucleoside reverse transcriptase inhibitors (NRTI), 1 (0-5) affecting non-nucleoside reverse transcriptase inhibitors (NNRTI) and 10 (0-18) responsible for resistance against protease inhibitors (PI). Enfuvirtide resistance mutations were found in 20% of the population. [10]. Genotypic and phenotypic resistance analyses revealed that 44% of the study population had an overall susceptibility score (OSS; derived from combined genotypic and phenotypic data) of <2 antiretroviral drugs. Patients were randomized in a 2:2:1 fashion to three treatment arms: MVC once daily (qd) plus OBT, MVC twice daily (bid) plus OBT or placebo plus OBT.

The 24-week results indicate significantly better efficacy in patients treated with MVC (qd or bid) + OBT vs. placebo + OBT [8, 9]. Further analysis demonstrated that a higher proportion of patients achieved HIV viral loads <400 and <50 copies/ml when MVC was administered twice vs. once daily [11].

An additional analysis of treatment response by drugs used in the OBT revealed that combining maraviroc with enfuvirtide or lopinavir/r (in absence of respective resistance mutations) increased the probability of achieving a viral load below the threshold of detection if these drugs were given for the first-time to a patient [12].

Another double-blind randomized placebo-controlled trial (A4001029) investigated the effects of maraviroc in treatment-experienced patients carrying X4 or R5/X4 dual/mixed-tropic viruses. This study focussed on safety parameters of MVC when used in patients expected to have no relevant viral load response to a CCR5 antagonist. The 190 enrolled patients were randomised in a 1:1:1 fashion to three treatment arms of MVC bid, MVC qd or placebo, each plus OBT. Baseline patient characteristics were similar to the MOTIVATE trials except for a lower CD4 cell count (median <50 cells/mm^3 in all three treatment arms) and a lower proportion of patients with an OSS <2 (26,9% in this trial). Analysis of treatment results did not show statistically significant differences between study arms regarding the change of viral load at week 24 versus baseline. Interestingly, the MVC bid + OBT group showed a larger increase of CD4 cell counts vs. baseline than the OBT + placebo arm (+62 vs. +36 cells/mm3), the difference being significant with a p-value of 0.04 [10, 13].

To summarize these studies, MVC exhibits favourable virological and immunological effects in pretreated HIV-infected patients with triple-class failure and CCR5 tropic viruses. As expected from the mechanism of action, a significant effect of MVC on viral load was not seen in patients with X4 or dual/mixed-tropic viruses. However, increased CD4 cell counts were observed in these patients while on MVC. MVC was well tolerated in treatment-experienced HIV patients.

Potential mechanisms of therapeutic failure are a relevant issue to be considered in antiretroviral therapy of treatment-experienced patients. In the case of CCR5 antagonists failure may occur due to i) a shift in the predominant viral coreceptor use from CCR5 to CXCR4, and ii) the development of "true" resistance involving mutations in the viral gp120 surface glycoprotein.

Approximately 55% of patients (63 of 115) with virological failure of a MVC-based regimen in the MOTIVATE trials showed a shift in the viral tropism from R5 to X4 or R5/X4, compared to 4.5% in the placebo + OBT arms [10]. Clonal analysis of viruses from patients who failed a MVC-regimen in these trials did not reveal evidence of a true tropism switch, in terms of R5 viral clones mutating to acquire the capacity to use X4 or both coreceptors [14, 15]. Rather, the investigators observed a tropism shift induced by selection of preexisting CXCR4-using clones which were detected post hoc at low numbers in the pre-treatment virus population [16].

Additionally, there is some evidence that "true" resistance to MVC can emerge on therapy. MVC is a non-competitive inhibitor of HIV´s binding to CCR5. By attaching itself to a specific pocket in the transmembrane region of CCR5, MVC induces a conformational change in the CCR5 protein structure, thereby preventing a productive interaction of the virus with its coreceptor. Resistance may emerge through substitution or deletion of amino acids in the V3 loop of the HIV-1 envelope glycoprotein gp120. Viruses with relevant mutations in the V3 loop are able to recognize CCR5 in the altered conformation induced by MVC and bind to the coreceptor with MVC attached to it [17]. In the MOTIVATE studies, viruses from 5 patients failing a MVC-containing regimen had developed mutations in the V3 loop sequences while remaining CCR5-tropic. Further genetic analyses in viral isolates from 4 of the 5 patients were performed, but a genetic resistance algorithm could not be derived from these data [10]. The MVC-resistant phenotype was not associated with a consistent pattern of changes in the viral gp120 amino acid sequence between different patients. Further investigations should be conducted on these issues.

VICRIVIROC

Besides MVC, several other promising CCR5 inhi-

bitors are currently being developed. The second most advanced agent is vicriviroc (VVC; Schering-Plough). Vicriviroc exhibited antiviral efficacy in patients infected with R5 viruses in an early phase 2 trial examining the effects of VVC monotherapy over 14 days [18].

The subsequent clinical trial investigating VVC in therapy-naive patients was stopped due to potential inferiority of the VVC-containing regimen versus the control group [19]. In contrast, ACTG 5211, a 24-week randomized double-blind placebo-controlled phase 2 study in treatment-experienced patients carrying R5 viruses, has been completed. Results were promising, as the viral load decline seen after 24 weeks was –1.51, –1.86 and –1.68 $\log_{10}$ copies/ml in the three VVC dosing arms of 5 mg, 10 mg and 15 mg, respectively. The viral load in the placebo arm changed by only –0.29 $\log_{10}$ [20]. The explanation for the success is the boosting effect of ritonavir. The study design of ACTG 5211 required a ritonavir-containing regimen which boosted the VVC into efficient plasma levels. Consequently, in June 2007, a phase 3 trial sponsored by Schering-Plough was started in several centers in the US. Patients eligible for this study are treatment-experienced, exhibit resistances in at least two classes of drugs (NRTI, NNRTI and/or PI) and carry CCR5-tropic HIV-1 viruses. Results will not be available before mid-year 2008.

Other CCR5 Antagonists

The third candidate CCR5 inhibitor was aplaviroc, discovered and investigated by GlaxoSmithKline [21]. Unfortunately, however, aplaviroc was associated with some severe liver toxicity in early trials and all studies including a phase 3 trial in treatment-experienced patients were discontinued.

Further new agents in this class include TAK-652 and INCB9471. TAK-652 is a derivative of TAK-779, the first CCR-5 inhibitor discovered by Takeda Pharmaceuticals, Japan [22]. This drug is still in preclinical development and there are no data available on its use in patients including pretreated individuals [23]. For INCB9472 developed by Incyte Corp., USA, recently published data of a small phase 2a monotherapy trial show good antiviral activity in patients harbouring R5 viruses [24]. More advanced clinical trials are planned.

Conclusion

Various other CCR5 inhibitors are currently being developed. As of today, none of them has reached the stage of clinical trials in treatment-experienced HIV-infected patients.

Most antiretroviral agents exhibit drug interactions that deserve attention to avoid inappropriate drug exposure. All small-molecule CCR5 antagonists are substrates of the hepatic CYP450 metabolic system which is of crucial importance for HIV therapy with respect to the boosting of protease inhibitors. Ritonavir as well as other PIs inhibit the CYP450 isoenzyme CYP3A4, while efavirenz induces its expression. Being substrates of CYP3A4, CCR5 antagonists are affected by these drugs, therefore requiring appropriate dose adjustments [10, 25, 26]. Furthermore, treatment-experienced patients with advanced stages of HIV-disease frequently receive additional comedications. Their potential interference with the pharmacokinetics of CCR5 antagonists must be kept in mind.

In conclusion, the new class of CCR5 antagonists that inhibit viral cell entry by blocking the CCR5 coreceptor will likely represent an important addition to the armamentarium of antiretroviral drugs. They will provide new treatment opportunities for patients with multiple-class failure carrying CCR5-tropic viruses. Patients with X4 or dual/mixed-tropic viral populations will not be treated with this class of agents, but may benefit from other newly developed agents such as integrase inhibitors or novel members of the established antiretroviral classes.

References

1. Brumme ZL, Goodrich J, Mayer HB, Brumme CJ, Henrick BM, Wynhoven B, Asselin JJ, Cheung PK, Hogg RS, Montaner JS, Harrigan PR. Molecular and clinical epidemiology of CXCR4-using HIV-1 in a large population of antiretroviral-naive individuals. J Infect Dis. 2005 Aug 1;192(3):466-74.
2. Moyle GJ, Wildfire A, Mandalia S, Mayer H, Goodrich J, Whitcomb J, Gazzard BG. Epidemiology and predictive factors for chemokine receptor use in HIV-1 infection. J Infect Dis. 2005 Mar 15;191(6):866-72.
3. Demarest J, Sparks S, Watson C, McDanal C, Kenakin TP, Shibayama S (2004). Prolonged and unique binding of a novel CCR antagonist, 873140. Abstract H-211, 44th ICAAC 2004, Washington.
4. Whitcomb JM, Huang W, Fransen S, Wrin T, Paxinos E, Toma J, Greenberg M, Sista P, Melby T, Matthews T, DeMasi R, Heilek-Snyder G, Cammack N, Hellmann N, Petropoulos C (2003). Analysis of Baseline Enfuvirtide (T20) Susceptibility and Co-receptor Tropism in Two-phase III Study Populations. 10th Conference on Retroviruses and Opportunistic Infections, Boston 2003; Abstract 557
5. Paxinos EE, Fransen S, Huang W, Wrin T, Whitcomb JM (2002). Measuring HIV-1 co-receptor tropism using a recombinant virus assay. Abstract H-2040, 42nd ICAAC 2002, San Diego.
6. Wilkin T, Su Z, Kuritzkes D, Hughes M, Flexner C, Gross R, Coakley E, Greaves W, Godfrey C, Gulick R (2006). Co-receptor Tropism in Patients Screening for ACTG 5211, a Phase 2 Study of Vicriviroc, a CCR5 Inhibitor. 13th Conference on Retroviruses and Opportunistic Infections, Denver 2006; Abstract 655
7. Fätkenheuer G, Pozniak AL, Johnson MA, Plettenberg A, Staszewski S, Hoepelman AI, Saag MS, Goebel FD, Rockstroh JK, Dezube BJ, Jenkins TM, Medhurst C, Sullivan JF, Ridgway C, Abel S, James IT, Youle M, van der Ryst E. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1. Nat Med 2005, Nov;11(11):1170-2.
8. Lalezari J, Goodrich J, DeJesus E, Lampiris H, Gulick R, Saag M, Ridgway C, McHale M, van der Ryst E, Mayer H (2007). Efficacy and Safety of Maraviroc plus Optimized Background Therapy in Viremic ART-experienced Patients Infected with CCR5-tropic HIV-1: 24-Week Results of a Phase 2b/3 Study in the US and Canada. 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles 2007; Abstract 104
9. Nelson M, Fätkenheuer G, Konourina I, Lazzarin A, Clumeck N, Horban A, Tawadrous M, Sullivan J, Mayer H, van der Ryst E (2007). Efficacy and Safety of Maravi-

roc plus Optimized Background Therapy in Viremic, ART-experienced Patients Infected with CCR5-tropic HIV-1 in Europe, Australia, and North America: 24-Week Results. 14th Conference on Retroviruses and Opportunistic Infections, Los Angeles 2007; Abstract 104a.
10. Pfizer Inc. Maraviroc Tablets NDA 22-128, Antiviral drugs advisory committee (ADVAC) briefing document, April 24, 2007 (www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4283b1-01-Pfizer.pdf , accessed Aug. 16, 2007)
11. Gulick RM, van der Ryst E, Lampiris H, Fätkenheuer G, Raffi F, Lalezari J, Sullivan J, Tawadrous M, Konourina I, Goodrich J, Mayer H (2007). Efficacy and safety of once-daily (QD) compared with twice-daily (BID) maraviroc plus optimized background therapy (OBT) in treatment-experienced patients infected with CCR5-tropic-HIV-1: 24-week combined analysis of the MOTIVATE 1 and 2 studies. 4th Conference on HIV Pathogenesis, Treatment and Prevention, Sydney 2007, Abstract WEPEB116LB.
12. van der Ryst E, Cooper D, Konourina I, Saag M, Goodrich J, Tawadrous M, Simpson P, Sullivan J, Westby M, Mayer H (2007). Efficacy of Maraviroc in combination with at least one other potent new antiretroviral drug: 24-week combined analysis of the MOTIVATE 1 and 2 studies. 4th Conference on HIV Pathogenesis, Treatment and Prevention, Sydney 2007, Abstract WEPEB115LB.
13. Mayer H, van der Ryst E, Saag M, Clotet B, Fatkenheuer G, Clumeck N, Turner K, Goodrich JM (2006). Safety and Efficacy of Maraviroc (MVC), a Novel CCR5 Antagonist, When Used in Combination with Optimized Background Therapy (OBT) for the Treatment of Antiretroviral-Experienced Subjects Infected with Dual/Mixed-Tropic HIV-1: 24-Week Results of a Phase 2b Exploratory Trial. 16th Internationam AIDS Conference, Toronto 2006, Abstract THLB0215
14. Dejucq N, Simmons G, Clapham PR. T-cell line adaptation of human immunodeficiency virus type 1 strain SF162: effects on envelope, vpu and macrophage-tropism. J Gen Virol 2000 Dec;81(Pt 12):2899-904.
15. Harrowe G, Cheng-Meyer C. Amino acid substitutions in the V3 loop are responsible for adaptation to growth in transformed T-cell lines of a primary human immunodeficiency virus type 1. Virology 1995 Jul 10;210(2):490-4.
16. Westby M, Lewis M, Whitcomb J, Youle M, Pozniak AL, James IT, Jenkins TM, Perros M, van der Ryst E. Emergence of CXCR4-using human immunodeficiency virus type 1 (HIV-1) variants in a minority of HIV-1-infected patients following treatment with the CCR5 antagonist maraviroc is from a pretreatment CXCR4-using virus reservoir. J Virol. 2006 May;80(10):4909-20.
17. Westby M, Smith-Burchnell C, Mori J, Lewis M, Mosley M, Stockdale M, Dorr P, Ciaramella G, Perros M. Reduced maximal inhibition in phenotypic susceptibility assays indicates that viral strains resistant to the CCR5 antagonist maraviroc utilize inhibitor-bound receptor for entry. J Virol. 2007 Mar;81(5):2359-71.
18. Schurmann D, Fätkenheuer G, Reynes J, Michelet C, Raffi F, van Lier J, Caceres M, Keung A, Sansone-Parsons A, Dunkle LM, Hoffmann C. Antiviral activity, pharmacokinetics and safety of vicriviroc, an oral CCR5 antagonist, during 14-day monotherapy in HIV-infected adults. AIDS. 21(10):1293-1299, June 2007.
19. Greaves W, Landovitz R, Fatkenheuer G, Hoffmann C, Antunes F, Angel J, Boparai N, Knepp D, Keung A, Dunkle L (2006). Late Virologic Breakthrough in Treatment-naive Patients on a Regimen of Combivir + Vicriviroc. 13th Conference on Retroviruses and Opportunistic Infections, Denver 2006; Abstract 655
20. Gulick RM, Su Z, Flexner C, Hughes MD, Skolnik PR, Wilkin TJ, Gross R, Krambrink A, Coakley E, Greaves WL, Zolopa A, Reichman R, Godfrey C, Hirsch M, Kuritzkes DR. Phase 2 Study of the Safety and Efficacy of Vicriviroc, a CCR5 Inhibitor, in HIV-1-Infected, Treatment-Experienced Patients: AIDS Clinical Trials Group 5211. J Infect Dis. 2007 Jul 15;196(2):304-12.
21. Lalezari J, Thompson M, Kumar P, Piliero P, Davey R, Patterson K, Shachoy-Clark A, Adkison K, Demarest J, Lou Y, Berrey M, Piscitelli S. Antiviral activity and safety of 873140, a novel CCR5 antagonist, during short-term monotherapy in HIV-infected adults. AIDS. 2005 Sep 23;19(14):1443-8.
22. Baba M, Nishimura O, Kanzaki N, Okamoto M, Sawada H, Iizawa Y, Shiraishi M, Aramaki Y, Okonogi K, Ogawa Y, Meguro K, Fujino M. A small-molecule, nonpeptide CCR5 antagonist with highly potent and selective anti-HIV-1 activity. Proc Natl Acad Sci U S A. 1999 May 11;96(10):5698-703.
23. Baba M, Miyake H, Wang X, Okamoto M, Takashima K. Isolation and characterization of human immunodeficiency virus type 1 resistant to the small-molecule CCR5 antagonist TAK-652. Antimicrob Agents Chemother. 2007 Feb;51(2):707-15.
24. Cohen C, DeJesus E, Mills A, Pierone, Jr. G, Kumar P, Ruane P, Elion R, Fusco G, Levy R, Solomon K, Erickson-Viitanen S (2007). Potent antiretroviral activity of the once-daily CCR5 antagonist INCB009471 over 14 days of monotherapy. 4th Conference on HIV Pathogenesis, Treatment and Prevention, Sydney 2007, Abstract TUAB106.
25. Anti-HIV agents. Maraviroc--absorption and drug-interaction issues. TreatmentUpdate. 2007 Mar-Apr;19(3):5
26. Strizki JM, Tremblay C, Xu S, Wojcik L, Wagner N, Gonsiorek W, Hipkin RW, Chou CC, Pugliese-Sivo C, Xiao Y, Tagat JR, Cox K, Priestley T, Sorota S, Huang W, Hirsch M, Reyes GR, Baroudy BM. Discovery and characterization of vicriviroc (SCH 417690), a CCR5 antagonist with potent activity against human immunodeficiency virus type 1. Antimicrob Agents Chemother. 2005 Dec;49(12):4911-9.

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Address for correspondence:
Thore Lorenzen
ifi-Institut
am AK St. Georg, Haus K
Lohmühlenstraße 5
20099 Hamburg
Germany
Tel.: +49 40 181885 3785

Curriculum Vitae

Thore Lorenzen

Thore Lorenzen received his graduation at medical school in Hamburg and entered a research fellowship at the interdisciplinary HIV outpatient department of St. George's Hospital in Hamburg in 1996. His main fields of interest were dermatological aspects of HIV infection as well as other sexual transmitted infections. Additionally, in 2000 he specialised in the field of drug addiction. Afterwards he joined the ifi-Institute as a consultant physician. He participated in several clinical trials as investigator. Actually, his research interests focus on mechanisms of therapeutic failure in HIV-infection and on new strategies of treatment.

Curriculum Vitae

Albrecht Stoehr

Albrecht Stoehr was born in 1954. He received his graduation in 1983 and specialized in internal medicine in the following years. Since 1987 his clinical and scientific works focus in the field of HIV and infectious diseases. In 2000 Dr. Stoehr co-founded the ifi-Institute with Prof. Plettenberg and is director of the institution. Additionally he is consultant for infectious diseases in several hospitals in Hamburg. Dr. Stoehr has remarkable experience in the treatment of HIV-infection and is investigator in multiple clinical trials concerning this issue.

Curriculum Vitae

Irene Walter

Irene Walther was born in 1980. She studied construction engineering and biomedical documentation in Hamburg and Hanover and graduated about risk factors for breast cancer. She is experienced in statistics, epidemiology and public health. In 2004 and 2005 she dealt with medical quality management and gained experience in planning and reviewing clinical trials. She entered the ifi-Institute in 2006 and is responsible for data management, statistics and study coordination. Her special interests are cohort studies and electronic data administration.

CURRICULUM VITAE

Andreas Plettenberg

Andreas Plettenberg is a professor of medicine at the University of Hamburg and he is head of the ifi-Institute for interdisciplinary medicine since 2000. He started to specialize in dermatology, venerology and infectious diseases in 1985. Besides HIV he is interested in the field of STI and rare dermatological infections. Since 1988 Prof. Plettenberg has conducted umpteen clinical trial concerning dermatology, infectious diseases and HIV-infection. He is member of several advisory boards and committees and works closely with the public authorities in Germany.