Eur J Med Res (2007) 12: 441-452

TREATMENT WITH CCR5 ANTAGONISTS: WHICH PATIENT MAY HAVE A BENEFIT?

M. C. Mueller, J. R. Bogner

Department of Infectious Diseases, Medizinische Poliklinik, University Hospital of Munich, Campus Innenstadt; Germany

Abstract
The concept of CCR5 antagonists introduces an additional molecular target. Maraviroc (MVR) is approved by the FDA for use in HIV-1 infected patients for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1 who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. Tropism and treatment history should guide the use of MVR. Data from clinical trials show significant efficacy of MVR for patients with pre-treatment and multiple class failure. Additional clinical data show a CD4 reconstitution that is more pronounced than with comparator in treatment naïve and in late stage patients even without CCR5-tropic virus indicating patients in earlier stages and even patients without CCR5 testing will benefit from MVR. MVR is not licensed for treatment naïve patients but it has a high potential for further development in this patient group. It shows better immunological reconstitution than efavirenz.

Pooled safety data from all available trials shows good short term tolerability. Caution is needed in hepatitis co-infection with pre-existing liver damage and in patients with heart failure.

Isolates from different geographic regions differ in coreceptor usage. Summarizing knowledge on HIV-1 subtypes and CCR5 tropism shows that in principle all subtypes are susceptible to MVR. However, in subtypes A and D dualtropic and alternative coreceptor use were found. Clinical efficacy in patients from regions with A and D predominance should be studied in future trials.

In conclusion, MVR will be of benefit for patients in various treatment situations and regions.

Key words: HIV-1, Maraviroc, inhibitor, antiretroviral, CCR5, CXCR4, BOB, GPR15, CXCR6, BONZO, coreceptor, tropism, subtype A, subtype B, subtype C, subtype D, subtype E, safety, efficacy, side effects, toxicity, therapy-naïve, therapy-experienced, Motivate

Abbreviations: ARV: antiretrovirals; NSI: non-syncytium-inducing; SI: syncytium-inducing; RH: rapid replicating; SL: slow replicating; M-tropic: macrophage tropic; T-tropic: T-cell-line tropic; MVR: Maraviroc; CYP3A4: cytochrome P450 3A4; OBT: optimized background therapy

INTRODUCTION

Therapy for Human Immunodeficiency Virus 1 (HIV-1) has been significantly advanced by the development of reverse transcriptase - and protease inhibitors. Early enthusiasm has however been tempered by long term toxicity, side effects, the emergence of cross resistance as well as complex dosing regimes. There is subsequently a growing need for well-tolerated and conveniently administered agents with a new mechanism of action.

The HIV-1 coreceptor chemokine receptor CCR5 is an especially attractive target in antiretroviral therapy as natural genetic absence and reduced expression of CCR5 results in a high resistance against HIV-1 infection and in a slower rate of disease progression respectively [1, 2]. The receptors for chemokines comprise a subfamily within the seven transmembrane domain G protein–coupled receptors superfamily where the two major classes are the CXC chemokines and the CC chemokines. Chemokines are small proteins with chemotactic activity for leukocytes. They play prominent roles in leukocyte activation and trafficking to sites of inflammation [3]. Chemokine receptors CCR5 and CXCR4, which are generally considered to be the most important HIV-1 coreceptors [4], play a crucial role in HIV-1 cell entry. The binding of HIV-1 surface protein gp120 to CD4 induces subtle conformational changes in gp120 which leads to exposure of structural elements of the V3 loop of gp120. The interaction between V3 loop and coreceptors in turn induces a structural rearrangement of gp41 which is then able to insert fusion peptide region into the target cell membrane. This brings the virus and cell membranes into close apposition in order to initiate fusion and ultimately the entry of the viral core into the target cell [5] (Fig.1)

Prior to identification of the critical role of chemokine receptors as coreceptors in the cellular entry, three classification systems of HIV tropism were used simultaneously. They divided HIV-isolates in macrophage (M)-tropic or T-cell-line (T)-tropic, in syncytium-inducing (SI) or non-syncytium-inducing

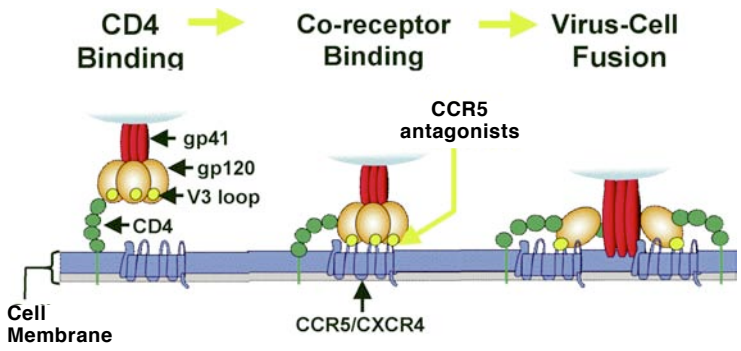

Fig. 1. Steps in HIV entry into target cells (Adapted from Moore JP, et al. Proc Natl Acad Sci U S A. 2003;100:10598-10602).

(NSI) and in slow (SL) or rapid/high (RH) replicating. In 1998 Berger et al. suggested a new classification which divides HIV-1 variants according to their coreceptor usage into those that exclusively use CCR5 (R5 or CCR5-tropic viruses), those that exclusively use CXCR4 (X4 or CXCR4-tropic viruses) and those that can use either receptors (dualtropic or R5X4 viruses) [6]. R5 viruses are M-tropic and non-syncytium-inducing, X4 viruses are T-tropic and syncytium-inducing and R5X4 viruses are M- and T-tropic and syncytium-inducing. In order to simplify the nomenclature, coreceptors which were considered to be used in a minor degree such as CCR2b, CCR3, BOB/GPR15, CXCR6 (Bonzo) etc. were not included in this classification [6].

Since the time of discovery of CCR5 as a potential target of antiretroviral therapy in 1996 [3], several CCR5-blocking agents have progressed to phase III clinical trials in less than ten years. In the present, one of them, Maraviroc, is the first to gain approval by the FDA in August 2007. Approval was declared for "treatment of adults infected with CCR5-tropic HIV-1 strain".

While trials used as a base for approval were performed in patients with advanced treatment (salvage) the question arises whether benefit from this new medication will be restricted to patients with treatment experience. To give an answer to the question –"which patient may have a benefit" the existing preclinical and clinical data about safety, efficacy, side effects and long term toxicity of Maraviroc in therapy naïve and – experienced patients are reviewed in this manuscript. In terms of coreceptor usage, clinical efficacy and safety issues the answer to this question will show that Maraviroc is not only a new dimension in HIV therapy but includes opportunities and questions deserving further studies.

Is Maraviroc a Therapy for all HIV-infected Individuals?

The antiviral effect of Maraviroc depends on the presence of exclusively CCR5-tropic HIV-1 strains in the infected individual because they show no effect on viral load when dualtropic or CXCR4-monotropic viruses are present [7]. For this reason the impact of Maraviroc on antiretroviral therapy depends to a high degree of the prevalence of R5 viruses in the total HIV-1 positive population. Testing for HIV-1 tropism before starting Maraviroc therapy can guide therapy and will select for patients with the "target" virus-type.

The Role of Coreceptor Usage in the Maraviroc Therapy

CCR5 Tropism Assay

There are two phenotypic tropism assays commercially available, both of which are based on phenotypic drug resistance assays [8, 9, 10]: Tropism Recombinant Test (TRT) (VIRalliance, Paris, France) [11] and Trofile (Monogram Biosciences, San Francisco, California, USA) [12]. Both assays use patient plasma-derived viral envelope sequences to construct either replication-competent or replication-defective viruses, respectively. These viruses are then used to infect engineered CD4+ target cell lines expressing either CXCR4 or CCR5, which permits determination of viral tropism by the expression of a reporter gene (β-galactosidase in TRT, and luciferase in Trofile) [10, 11] (Fig 2).

In comparison with MT-2 cell assay and *in vitro* assays with reporter cell lines to determine viral coreceptor usage recombinant phenotypic tropism assays appear to be faster and less resource intensive [13]. The recombinant phenotypic tropism assays remains to be evaluated and several questions seem still to need clarification: What is the effect of different target cell types and receptor/coreceptor expression levels on the determination of tropism? Is the test sensitive enough to detect minor species within the viral population? In one study recombinant phenotypic tropism assay failed in 298 of 861 samples (35%) [13], which leads to the question if recombinant phenotypic tropism assays will be an effective instrument to assess tropism.

Prevalence of CCR5-tropic HIV-1 Strains

R5 strains are generally found at the time of HIV-1 acquisition and in the early stages of infection. The transmission of CXCR4-tropic viruses appears to be constrained [14]. The prevalence of R5X4 virus or X4 virus increases with time after infection and is related to low CD4 cell count, high RNA level and decreasing natural killer cell count [13]. As an example, Hunt et al. demonstrated that in therapy-naïve persons with CD4 cell counts >300 cells/mm3 and HIV-1 RNA loads <5000 copies/ml, 42 (89%) of 47 of samples

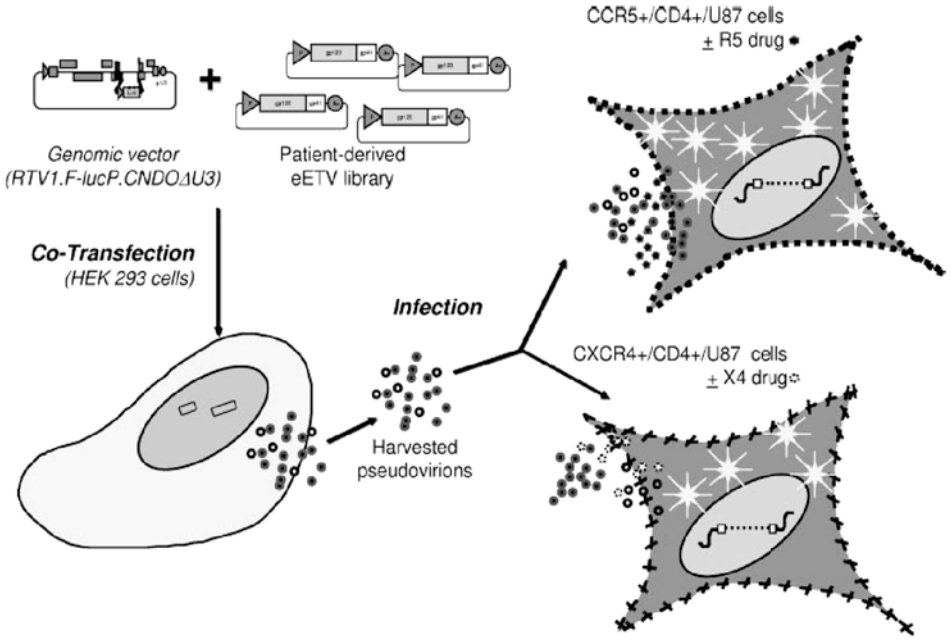

Fig. 2. Schematic diagram of a recombinant tropism assay. Pseudovirus particles carrying envelope glycoproteins derived from the plasma virus are produced by transfecting producer cells with the purified envelope expression vector library and an HIV-1 genomic vector lacking the envelope-encoding region and containing a luciferase gene. Luciferase protein catalyzes luciferin oxidation to generate light, and is used to measure the ability of the pseudoviruses to infect target cells expressing CD4 and either CXCR4 or CCR5 (From: Whitcomb, J.M., et al. Antimicrobial Agents and Chemotherapy, Feb. 2007, p. 566-575).

contained CCR5-using virus, whereas, for persons with CD4 cell counts <50 cells/mm3 and HIV-1 RNA loads >100,000 copies/ml, only 17 (55%) of 31 of samples contained CCR5-using virus [13] (Fig. 3).

Comparing tropism in studies including therapy-naïve patients with those including HAART-experienced individuals demonstrates a significantly higher prevalence of R5X4 viruses in HAART-experienced individuals (34% to 50%) [15, 16] in contrast to the prevalence of dualtropic viruses in therapy naïve individuals (12 and 19%) [17, 18]. This enrichment of dualtropic and CXCR4-using viruses under antiretroviral treatment appears to be explained by lower pre-treatment nadir and not as an effect of HAART itself [19].

Most of the studies cited above were performed in industrialized countries where HIV-1 subtype B prevails. Little is known about coreceptor usage in HIV-1 subtypes other than subtype B. HIV-1 subtype C is widespread in southern Africa as well as in India and is the most extensive HIV-1 subtype globally [20] (Fig. 4).

In a study of Casper et al. evolution of coreceptor use in HIV-1 isolates of 24 vertically infected children was analysed [21]. The mothers of the children originated from numerous parts of the world and the children therefore carried five different env subtypes (nine A, five B, four C, three D and one G) and one circulating recombinant form, CRF01_AE (n = 2). X4 virus was mainly isolated from the children carrying subtypes A, B, D, or CRF01_AE after increasing time of infection but this was not the case from children infected with subtype C. These findings are in agreement with results from earlier studies which demon-

Study/Source	Population	N	R5	X4	R5/X4
Homer cohort[a]	Naive	979	82%	<1%	18%
C & W cohort[b]	Naive	402	81%	<1%	19%
Demarest[c]	Naive	299	88%	0%	12%
TORO 1/2[d]	Experienced	612	62%	4%	34%
ViroLogic[e]	Experienced	>2000	48%	2%	50%
ACTG 5211[f]	Experienced	391	49%	4%	47%

[a]Brumme ZL, et al. J Infect Dis. 2006;192:466-474.
[b]Moyle GJ, et al. J Infect Dis. 2005;191:866-872.
[c]Demarest J, et al. ICAAC 2004; Abstract H-1138.
[d]Whitcomb JM, et al. CROI 2003; Abstract 557.
[e]Paxinos EE, et al. ICAAC 2002; Abstract 2040.
[f]Wilkin T, et al. CROI 2006; Abstract 655.

Fig. 3. Data from a number of clinical cohort studies illustrates that HIV-1 (prevailing subtype B) is predominantly (>80%) CCR5-tropic in treatment-naive patients with essentially no CXCR4-tropic and between 12% and 18% dualtropic virus. In treatment-experienced patients prevalence of dualtropic virus increases. Pure X4 tropism remains rare (From: Pfizer: Full public slide deck for external use).

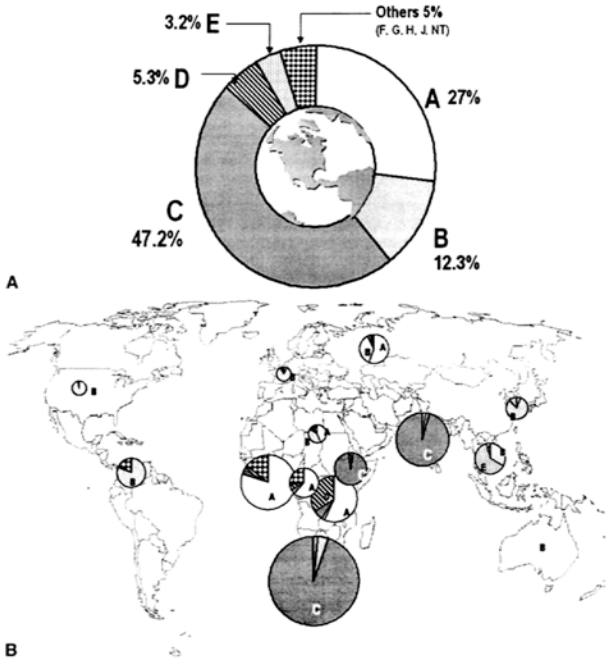

Fig. 4. A: Estimated incidence of HIV-1 env subtypes in the year 2000. B: Estimated distribution of new HIV-1 infections by env subtypes and regions in the year 2000. From: Osmanov: J Acquir Immune Defic Syndr, Volume 29(2).February 1, 2002. 184-190.

strate an overwhelming predominance of CCR5-tropic viruses in subtype C at various stages of disease, even among AIDS patients [22, 23, 24]. Although a few CXCR4-tropic viruses have been reported elsewhere [25, 26], CXCR4-tropism among subtype C is less frequent than among subtype B viruses. These observations have been made among untreated patients as drug therapy is usually scarce in the areas where subtype C predominates. In a study of Johnston et al. a high frequency of X4 viruses was identified in HIV-1 subtype C isolates of individuals enrolled in a treatment access program in Zimbabwe, all of whom had prolonged ART drug exposure [27]. The authors conclude from these findings that antiretroviral treatment may create an environment for the emergence of CXCR4 tropism in HIV-1 subtype C virus.

In contrast to this, several studies showed a considerable dominance of X4 and R5X4 viruses in individuals infected with HIV-1 subtype D [22, 21]. In a study of Tscherning et al. out of 14 subtype D virus isolates, 6 were CCR5-tropic but 8 were exclusively CXCR4-tropic and none showed dual tropism. In comparison to the other subtypes analyzed in this study, X4 virus was clearly overrepresented. Uni- and multivariate analyses indicated that these subtype-specific differences in coreceptor usage were not due to differences in clinical status, CD4 counts, or treatment [22]. In another trial none of 33 subtype A or 10 A/D-recombinant viruses used the CXCR4 coreceptor. On the contrary, nine (36%) of 25 subtype D viruses were dual-tropic [28]. In the study of Casper et al. cited above 4 children of 14 with subtype A, D, or CRF01_AE developed X4 virus in the course of the infection, whereas none of 10 children with subtype B, C, or G developed X4 virus. These findings are in agreement with the results of a study from Uganda which compared prevalence of R5 virus in HIV-1 subtype A and D in therapy-naive patients. In non-AIDS patients with subtype A in 19 of 23 (83%) isolates R5 viruses were present whereas only in 15 of 27 (56%) of subtype D isolates R5 viruses were found [29]. On the other hand, in one trial analyzing 10 isolates of several subtypes all but one of subtype D isolates were non-syncytium-inducing, R5 viruses [30].

Menu et al. analyzed the isolates of 18 individuals infected with HIV-1 subtype E in Cambodia. R5 virus was predominant in patients of clinical stage B. Among 10 patients with AIDS five were carrying NSI virus. Menu concluded that "the tropism of Cambodian subtype E viruses isolated from patients at distinct stages of disease progression was similar to that reported for subtype B isolates" [31]. In a study which characterized coreceptor usage of HIV-1 subtype E in Bangkok none of 102 subtype E isolates used CXCR4 which confirms the predominance of R5 virus in HIV-1 subtype E, even when in this study the receptor usage was not correlated to stage of disease progression [32].

Usage of Alternative Coreceptors in HIV-1 Subtypes

As mentioned above, the two most important coreceptors in HIV-1 cell entry are CCR5 and CXCR4, and all HIV-1 isolates tested to date use one or both [4]. Growing complexity results from the findings that HIV-1 coreceptor activity is not limited to CXCR4 and CCR5. Current knowledge of the HIV-1 coreceptor repertoire includes several other human chemokine receptors and related Orphans as CCR1, CCR2b, CCR3, Bob/GPR15, CXCR6 (Bonzo), CCR8 and further still unknown coreceptors [3, 33, 34].

Coreceptor usage of HIV-1 other than CCR5 and CXCR4 is today still thought to be seldom and is contributed to mainly HIV-2 and simian immunodeficiency virus (SIV) group [35, 36]. In the last years increasing evidence is available which suggests that in particular the HIV-1 subtype A uses alternative coreceptors such as CXCR6 (Bonzo) and BOB/GPR15 [37, 21, 38, 39, 40] even in the early stages of infection [37, 38].

In a study in the Central African Republic viruses of 17 patients, all belonging to env subtype A, were isolated at various times after seroconversion and their coreceptor usage was examined. All isolates obtained soon after seroconversion used CCR5 and all but one isolates maintained their CCR5 usage in the course of infection. CXCR4 usage was limited to a few isolates and appeared generally in the late stages of the infection. Viruses of 13 patients were able to efficiently use BOB and/or CXCR6 (Bonzo) to establish a productive infection. In three patients BOB and CXCR6 (Bonzo) tropic viruses could be detected in the first isolates after seroconversion [37].

In another study coreceptor usage of isolated HIV-1 viruses were examined in samples of seropositive, asymptomatic pregnant women in Cameroon. Viruses were predominantly envelope subtype A and used coreceptor CCR5. 4 of 28 (14.2%) subtype A isolates

also used receptor CXCR6 (Bonzo) whereas none of four non subtype A isolate used CXCR6 (Bonzo) [39].

As utilization of BOB/GPR15 seemed to depend largely on cell surface expression level it remains to be elucidated if relevant target cells express BOB/GPR15 and CXCR6 (Bonzo) at levels that support virus replication. It has however been shown that BOB/GPR15 is expressed in lymphoid tissue. Thus, it cannot be excluded that usage of BOB/GPR15 may contribute to virus propagation [38].

Is Maraviroc a Therapy for all CCR5-tropic HIV-1 Subtypes?

Dorr, Macartney et al. performed an *in vitro* study of Maraviroc with 43 primary HIV isolates of various subtypes that were also exclusively CCR5-tropic [41]. These isolates were from various clades and diverse geographic origin and showed a geometric mean 90% inhibitory concentration of 2.1 nM. Moreover, Maraviroc was active against 200 clinically derived HIV-1 envelope-recombinant pseudoviruses. One hundred of these were derived from isolates resistant to existing drug classes. The mechanism of action of Maraviroc was investigated by cell-based assays using inhibition of binding of viral envelope, gp120, to CCR5 in order to prevent the membrane fusion events necessary for viral entry. Maraviroc did not affect CCR5 cell surface levels or associated intracellular signalling, confirming it as a functional antagonist of CCR5. In these studies Maraviroc did not show any detectable cytotoxicity. It was highly selective for CCR5. This was taken as a predictor of good clinical tolerability in humans.

A figure in the publication of Dorr and colleagues shows the geometric mean IC90s (and 95% confidence intervals) obtained for viruses grouped by different virus clades (Fig. 5): The overall geometric mean *in vitro* IC90 (the concentration at which 90% of viral replication is inhibited) for all 43 viruses was 2.1 nM. The conclusion was that "no "standard" exclusively CCR5-tropic subtype of HIV-1 appeared to have a significantly lower susceptibility to Maraviroc than any other".

A hybrid subtype which was called subtype E (CRF_01(AE)) showed a markedly greater susceptibility. This led to the question whether subtype E HIV might show a hypersusceptibility that could be used as a clinical advantage in patients with this subtype, e.g. from Asia.

All together, comprehensive studies about CCR5/CXCR4 prevalence and evolution in the course of infection were only conducted in the industrialized part of the world where env subtype B is predominant. Those studies show that the presence of R5 viruses, the imperative condition for Maraviroc virological efficacy, declines as time progresses after infection and eventually under prolonged ART exposure. This leads to the conclusion that it might be strategically better to use Maraviroc before salvage therapy and before advanced immunodeficiency in individuals infected with HIV-1 subtype B.

It has been widely accepted that coreceptor switch is uncommon in HIV-1 subtype C even in advanced stages of disease [22, 23, 24, 42, 43]. In subtype B contrarily up to 50% of viral isolates use CXCR4 in late stages of disease (see Fig. 3). This implicates that there are subtype specific differences in coreceptor usage. Coreceptor usage of other subtypes has been studied to a minor degree. HIV-1 subtype D appears to show a high prevalence of dualtropic and CXCR4 monotropic virus strains.

According to two studies from Cambodia [31] and Thailand [32] HIV-1 subtype E shows similar characteristics in coreceptor usage as subtype B.

Regarding subtype A, usage of alternative coreceptors has been examined in various studies [37, 21, 38, 39, 40]. In one trial about 50% of HIV-1 subtype A isolates used BOB, CXCR6 (Bonzo) or BOB and CXCR6 (Bonzo) in addition to CCR5 for cell entry. Almost all of them were able to efficiently use BOB and/or CXCR6 (Bonzo) to establish a productive infection [37]. Cilliers et al. demonstrated that viruses using BOB and/or CXCR6 (Bonzo) may establish a productive infection even when CCR5 and CXCR4 are blocked [33]. Under this condition standard pre-treatment tropism assay screening isolates only for CCR5- and CXCR4-tropism could result in a high percentage of treatment failure in patients infected with subtype A HIV-1 strains as tropism for BOB and CXCR6 (Bonzo) may remain undetected.

On the other hand the trials of coreceptor usage in different HIV-1 subtypes are not extensive and some are contradictory. Furthermore the studies were all performed *in vitro* so additional studies will therefore be required to evaluate the relevance of alternative

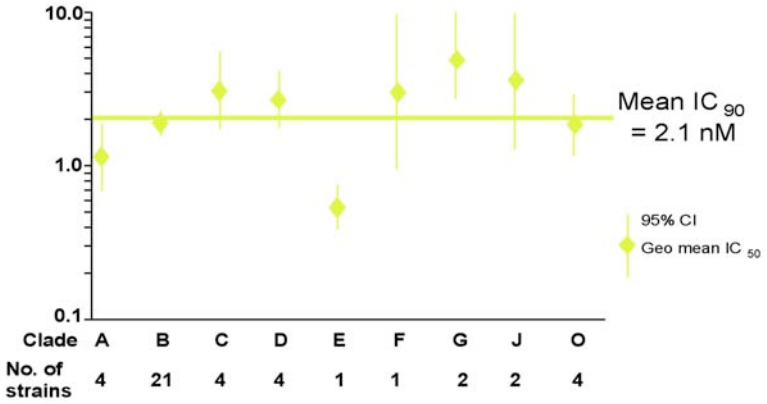

Fig. 5. Maraviroc potency against primary HIV-1 isolates in PBMCs: possible hypersusceptibility of HIV-1 subtype E (From: Pfizer: Full public slide deck for external use)

coreceptors usage *in vivo*. There is only limited data about F,G,H and J subtype available.

Nevertheless, CCR5-tropism presumed, Maraviroc has proven its efficacy in all HIV-1 subtypes. Preliminary data show a hint at pronounced susceptibility of subtype E.

Resulting from this data it can be said that Maraviroc might be of a significant interest for those regions where HIV-1 subtype B, C and E are the predominant strain even if its impact in regions with a pronounced prevalence of subtype A and D might be reduced. Maraviroc might require adapted treatment strategies according to the subtype prevalence in different regions of the world.

Efficacy of Maraviroc in Clinical Studies

Virological Efficacy in Asymptomatic HIV-infected Patients

After Maraviroc had been tested in healthy individuals without HIV infection (unpublished data, according to the paper of Fätkenheuer and colleagues) Fätkenheuer and colleagues carried out a set of two trials to investigate the antiviral efficacy of Maraviroc [44]. In order to study the effect of the drug alone, without combination of other antiretrovirals, they used a study design of monotherapy for 10 days. Both studies were placebo – controlled and randomized. 163 asymptomatic HIV-1 – infected patients were screened. About 50% were enrolled. Important reasons for exclusion were hepatic impairment, CD4 count below inclusion limit (250/µl), and a virus type not phenotypeable. Notably, 94% of the screened patients in this group (asymptomatic, Maraviroc- naïve) had a CCR5 – tropic virus. Oral treatment was administered as daily doses of 50mg, 100mg, 300mg, and 600mg or placebo. The difference between once daily dosing and two doses 12 hours apart was studied as well as the influence of food along with study medication. Eight patients per dose group were randomized. As expected, placebo was less effective as all dose groups of the study drug. At doses of 100 mg BID and more all study participants showed a more than one log10 virus load reduction at the time of VL nadir. The median time to VL nadir was 11 days. The average viral load reduction among HIV-positive people taking at least 200mg of Maraviroc a day was between 1.6 and 1.84 log. Using the 150mg dose twice daily was as effective in VL reduction as the 300mg once daily. At 150mg coadministration of food did reduce the AUC by roughly 50%, however, the Cmin was not altered. The authors interpreted their results in discussing that "taken together, these results imply that Maraviroc is likely to be suitable for QD dosing without food restrictions".

Because of concerns that selection pressure exerted by a CCR5 inhibitor towards emergence of CXCR4 tropic virus in this study also follow up typing of virus receptor use were carried out. Changes in virus tropism were found in two patients in a low dose group (100mg QD). In one patient the change was not persistent, whereas the X4 virus was detectable in the other patient through day 433 after therapy.

Tolerability of Maraviroc was good in all doses in these studies. There were only five side effects that were observed in more than one individual: headache, asthenia, dizziness, gingivitis, and nausea.

Efficacy in Antiretroviral Naïve Patients

Maraviroc was also tested in therapy naïve patients regarding its non-inferiority to Efavirenz both combined with Zidovudine and Lamivudine (ZDV/3TC) (Study 1026). In this phase 2b/3 trial a total of 917 patients was enrolled in three treatment arms: Maraviroc QD plus ZDV/3TC, Maraviroc BID plus ZDV/3TC, and Efavirenz plus ZDV/3TC. Patients with only R5 HIV-1, HIV RNA of more than 2000 copies/ml and exclusion of EFV, ZDV, or 3TC resistance were randomized. The primary endpoint was the percentage of patients with viral load below 400 and below 50 copies/ml at week 24 and week 48. Due to an interim analysis after 16 weeks of treatment, the Maraviroc QD arm has been stopped in January 2006 as prespecified criteria of non-inferiority between the Maraviroc QD treatment group and Efavirenz treatment group were not met. However, the data safety and monitoring board of the trial recommended a continuation of the Maraviroc twice-daily arm.

Data on 48 week efficacy were presented in 2007 at the IAS conference in Sydney by Saag and colleagues [45]: Baseline median CD4 count (241 and 254 cells/µl) and mean HIV-1 RNA (4.9 and 4.9 log10 copies/ml) were similar in the MVR-BID and EFV groups. More patients discontinued MVR-BID because of efficacy failure compared with EFV (11.9% versus 4.2%). On the other hand, fewer patients discontinued MVR-BID due to adverse events (4.1% versus 13.6%). Results for the important efficacy endpoints were as follows: HIV RNA below 400 copies/ml was achieved in 70.6% (MVR) versus 73.1% (EFV) of patients and HIV RNA below 50 copies/ml resulted in 65.3% (MVR) versus 69.3% (EFV). Immunological reconstitution was measured as a gain in CD4 cells versus baseline. Mean Change from baseline was 170/µl (MVR) versus 143/µl (EFV). The conclusion from this analysis was that non-inferiority of MVR-BID could be confirmed for the below 400 copies/ml but not the below 50 copies/ml endpoint. CD4 cell count increase for MVR-BID was more pronounced than for EFV. MVR-BID was better tolerated than EFV with fewer discontinuations due to adverse events, AIDS defining illnesses, and grade 3/4 adverse events.

From a theoretical point of view, the use of Maraviroc in a first line regimen can be regarded as a completely new concept in highly active ART. The utilisation of new targets aiming at reduction of the number of newly infected target cells should also be seen in the context of down – scaling the number of latently infected cells.

At present, there is no trial investigating the combination of Maraviroc with anything else than nucleosides (NRTIs). The combination of Maraviroc with non-nucleosides (NNRTIs), protease inhibitors (PIs) or even integrase- inhibitors would also be worth

while being tested. The concept of a nucleoside sparing regimen with a low number of pills could more easily be achieved with Maraviroc plus a non-nucleoside "backbone". This concept, however, is dependent on further long term experience with Maraviroc: Independently of the results of study 1026 the question remains, whether non-inferiority of Maraviroc against Efavirenz for achieving less than 400 copies/ml will lead to an approval for first line therapy without a second trial. Even when Maraviroc appears to be generally well tolerated it belongs still to a new class of antiretroviral drugs without any long term experiences being available.

Clinical Efficacy in Patients with Prior Therapy and Multiple Viral Pre-treatments (Salvage)

Two clinical trials have been set up in patients pretreated with all three conventional drug classes. In this situation the introduction of a compound with no cross–resistance is of importance to overcome virological treatment failure. The two trials addressing this situation are known under the encouraging name MOTIVATE 1 and MOTIVATE 2 (Trials 1027 and 1028, MOTIVATE 1 was conducted in USA/Canada and MOTIVATE 2 in Europe/Australia/USA). A total of 1075 patients were enrolled for these trials, 601 for MOTIVATE 1 and 474 for MOTIVATE 2.

Both trials were conducted using the same study design: a phase 2b/3 trial, multicenter, randomised, double blind study with randomisation in Maraviroc once (QD) or twice daily (BID) versus placebo. The dosage groups of Maraviroc were 150mg QD versus 150mg BID. Randomisation proportions were 2:2:1 (2 MVR QD: 2 MVR BID : 1 Placebo) and all patients received an optimized background therapy (OBT) according to a resistance assay at screening. At the time before enrolment each patient was tested for the presence of CCR5 – tropic virus. Only patients with CCR5 – tropic virus were to be enrolled for the study.

The results of the two trials were analysed separately and in a combined manner. The major outcome parameter virus load showed significantly better results in the MVR arms as compared to placebo.

The 24 week data for this study were presented at the 2007 IAS conference [46]. Roughly double as many patients achieved a virus load below detection limit as with MVR as compared to placebo. Overall virological response rates to a viral load less than 400 copies/ml were: 28% (Placebo + OBT), 55% (MVR QD + OBT), and 61% (MVR BID + OBT). Virological efficacy with response to less than 50 copies/ml was: 23% (placebo + OBT), 44% (MVR QD + OBT), and 45% (MVR BID + OBT). Patient numbers in this analysis were n = 209 (placebo + OBT), n = 414 (MVR QD + OBT), and n = 426 (MVR BID + OBT).

In another combined analysis of both studies, Elena van der Ryst presented data on efficacy when it was set in relation to genotypic, phenotypic and overall susceptibility scores to the concomitant OBT, as well as by first-time use of selected background drugs [47]. As expected, more patients with higher susceptibility scores reached an undetectable viral load as compared to those with lower scores. Patients receiving Maraviroc whose virus had no enfuvirtide or Lopinavir/r resistance mutations detected at screening, first-time use of enfuvirtide or Lopinavir/r increased the likelihood of achieving undetectable HIV-1 RNA. 53% of patients naïve for enfuvirtide use who received MVR BID achieved a viral load below 50 copies/ml at week 24 as compared to 36% in the placebo group.

This data clearly demonstrated that MVR use in a salvage situation is also more effective when combined with additional active drugs.

Another analysis of the combined MOTIVATE – data was conducted concerning patients with no active OBT compounds and with a very poor baseline situation [48]. This was a planned 24-week analysis of pooled data presented at the IAS Conference 2007. Even in patients with no active drugs in OBT (based on genotypic/phenotypic test results) the percentages of patients with a viral load of <50 copies/ml was achieved in 18% (MVR QD) and 29% (MVR BID) as opposed to only 3% in the placebo arm.

Similar results were found for patients with less than 50 CD4 cells/µl at baseline and for patients with a viral load of more than 100000 copies per ml: In the MVR QD arm 11% of patients with less than 50 CD4 cells/µl and in the MVR BID arm 29% hat a virus suppression below 50 copies/ml after 24 weeks, while in the placebo arm only 3% of patients showed the same efficacy. Overall, primary and secondary endpoint analyses in this trial demonstrated superior virologic and immunologic efficacy of each Maraviroc group vs. placebo. A greater number of patients in subgroups with poor baseline parameters receiving Maraviroc BID achieved virologic suppression .

Safety of Maraviroc

Side Effects of Maraviroc

Pooled analyses from a total of six phase 1/2a studies comprised a total of 259 healthy volunteers and HIV infected patients who had received Maraviroc [49]. The majority of the adverse events were graded as mild or moderate. Up to doses of 600mg per day the pattern of adverse events was similar to that of placebo. Only headache, nausea and flatulence occurred more frequently, but not statistically significantly more frequently, in the Maraviroc 300 mg group than in placebo.

Postural hypotension was a dose-limiting adverse effect in phase 1 studies with MVR. McHale et al. studied the dose – response relation regarding this AE. The incidence of postural hypotension at Maraviroc doses from <100 mg to 1200 mg was determined from all available data. No postural hypotension was seen at Maraviroc doses <600 mg (QD or BID). Thus, doses used in subsequent clinical trials and the dose for the upcoming approval of the compound are in a range where postural hypotension is no to be expected as a frequent side effect.

In electrocardiographic studies referenced by McHale et al. no evidence of clinically relevant prolongation of QTc F was reported. There is a substantial body of clinical and ECG data from all trials with

MVR investigating this issue.

In the same study the MVR effect on liver function tests was reported: ALT elevations were sporadic and not associated with Maraviroc dose or bilirubin elevations. All patients who experienced ALT elevations also had concurrent illnesses potentially associated with ALT elevations. Overall, elevations of liver function tests were not more frequent than in placebo patients and those patients with elevations more than 3 times of the upper limit of normal were found to have concomitant conditions which usually cause ALT elevation (e.g. EBV infection, food poisoning).

In the trial with therapy naïve individuals (1026) the grade 3 and grad 4 AE were more frequently reported in the comparator arm with Efavirenz than with MVR. Moreover, fewer malignancies occurred on MVR and the incidence of grade 3/4 transaminase abnormalities was similar between the two groups [45].

Pooled analyses of both MOTIVATE trials (studies 1027 and 1028) demonstrated similar safety profiles for BID and QD groups versus placebo, with no increased hepatotoxicity with Maraviroc compared to placebo, including hepatitis B and C co-infected patients, and no imbalance in malignancies (either AIDS or non-AIDS associated) .

Safety of Maraviroc in Patients with Non-R5 HIV-1

One pivotal study (study 1029) is underway to determine the safety and efficacy of MVR when it was added to an optimised regimen (OBT) in comparison with OBT alone, especially in patients with dual/mixed-tropic (D/M) infection [48].

Study 1029 is an ongoing, 48-week, randomized, double-blind, multicentric, placebo-controlled Phase 2b study of MVR in treatment-experienced (triple-class experience and/or dual-class-resistant HIV-1) patients with HIV-1 RNA of more than 5000 copies/ml and non-R5-tropic HIV-1 infection. Eligible patients were randomized 1:1:1 to one of three arms:

OBT (comprising 3–6 open-label antiretrovirals of which at least one is active and no more than one is an NNRTI) and placebo, OBT plus MVR 150 mg QD, or OBT plus MVR 150 mg BID.

Patients where OBT did not contain a PI or the NNRTI delavirdine, received doses of MVR 300 mg QD or BID according to their original randomization. Coreceptor tropism testing was performed in all patients with treatment failure and/or HIV-1 RNA of more than 500 copies/ml at screening, and at weeks 4, 8 and every 8 weeks after the first 8 weeks.

The primary endpoint of this analysis was the change from baseline to 24/48 weeks in viral load for patients with D/M-tropic HIV-1 at screening. Treatment failure was defined as any one of: an increase to more than three times baseline plasma HIV-1 RNA level at week 2 or thereafter, HIV-1 RNA decrease of less than 0.5 log10 at week 8, HIV-1 RNA less than 1.0 log10 decrease from baseline starting at week 8, in a patient who had previously achieved a more than 2.0 log10 decrease from baseline, an increase in HIV-1 RNA to more than 5,000 copies/ml in a patient previously confirmed to have undetectable levels of less than 400 copies/ml. These viral load criteria had to be confirmed by two consecutive measurements.

190 patients were randomized and 186 patients received at least one dose of study drug. 167 patients had D/M-tropic HIV-1 at screening and represented the primary study population.

At least 91% and 52% of patients in each arm of the study received a PI or enfuvirtide. The number of active drugs in the OBT was slightly greater in the MVR BID arm than in the other two arms. All patients who had more than four active drugs were in the MVR BID arm.

Baseline characteristics of the patients show that this was a group of patients with advanced HIV disease: the overall median baseline CD4 cell count was less than 50 cells/μl and the baseline viral load was at least 5 log10 HIV-1 RNA copies/ml for all three treatment arms.

Reduction of viral load from baseline to week 24 was similar for the MVR QD + OBT (–0.91 log10) and placebo + OBT treatment arms (–0.97 log10). It was more pronounced for the MVR BID arm (–1.20 log10) but this difference was not statistically significant.

For the analyses of the proportion of patients who achieved HIV-1 RNA below 400 copies/ml and HIV-1 RNA below 50 copies/ml, respectively, all patients who discontinued prior to week 24 were included as non-responders.

Immunological recovery as measured by the mean change in CD4 cells was greater for the MVR groups: +60 and +62 cells/μl, for QD and BID, compared to +35 cells/μl for placebo. Maraviroc was well tolerated in this advanced population with documented D/M HIV-1 infection. Superiority of either MVR dose added on to OBT, versus OBT alone, was not achieved. However, a more pronounced CD4 increase was found the MVR treated patients.

Upcoming trials might be necessary to investigate whether similar effects can also be achieved in patients groups with less advanced HIV infection.

Tropism Change under CCR-5 Antagonist Treatment

As CCR5/CXCR4 receptor tropism change is related to the acceleration of disease and to the advanced stages of disease during the natural evolution of HIV-1 infection, it was feared that the implementation of CCR5 antagonists might induce tropism change and therefore leading to an acceleration of disease progress. Indeed the phase III trial of Maraviroc established that more patients receiving Maraviroc than those receiving placebo had a change in tropism to a dualtropic or CXCR4-tropic virus at the time of failure [50], indicating that viruses can switch coreceptor preferences in patients on CCR5 antagonist treatment. In a phase II trial 62 HIV-1 positive individuals were treated with Maraviroc monotherapy for ten days. In 60 of 62 patients the circulating virus remained CCR5-tropic, whereas viruses of two patients demonstrated a change of tropism to CXCR4. The circulating virus did however revert to CCR5 tropism after

cessation of therapy. Furthermore the authors could demonstrate by phylogentic analysis of envelope clones from pre- and posttreatment time points that the CXCR4-using variants probably emerged by outgrowth of a pre-treatment CXCR4-using reservoir, rather than via coreceptor switch of a CCR5-tropic clone under selection pressure from Maraviroc [51]. Accordingly, Maraviroc did not select the X4 phenotype after lengthy serial passage through increasing Maraviroc concentrations of CCR5-tropic laboratory strains or primary isolates *in vitro* [52]. Finally it has not been possible to discern whether the appearance of new viral phenotypes precedes disease development or results as a consequence of it, even if isolated reports now suggest that CXCR4-using viruses may emerge as a consequence of developing immune deficiency [21].

Long Term Toxicity of Maraviroc

No data about long term toxicity over several years of Maraviroc is available. A potentialy low long term toxicity of Maraviroc might be derived from the fact that the 32 base pair deletion in both copies of the CCR5 gene, creating a non-functional receptor, appears not to be associated with an important defect of immune function; individuals who are homozygous for CCR5 Δ32 deletion have no shortening of life expectancy [53].

There is nevertheless certain data available indicating that Δ32 deletion affects the course of infectious diseases. In CCR5 deficient mice infected with M. tuberculosis or Listeria a greater T-cell response was observed compared to ccr5 $^{+/+}$ mice [54]. One study demonstrates an association of CCR5 Δ32 deletion with increased risk of symptomatic West Nile virus infection [55]. Thio et al. on the other hand demonstrated a protective effect of CCR5 Δ32 deletion in recovery from HBV infection. Amongst nine chronically infected individuals which were homozygous for the deletion, eight recovered from the infection [56]. The effect thus far of CCR5 inhibition on infectious disease is probably due to the diverse pathophysiological reactions of immune system to different pathogens not predictable.

Which Patient Characteristics May Influence Pharmacological Use of Maraviroc?

There is a wide range of pharmacokinetic studies with Maraviroc investigating various types of populations and different situations ranging from therapy – naïve patients to patients with the possibility of many interactions. Pharmacokinetic studies with Maraviroc have shown a rapid absorption with a Tmax of 0.5-4.0 hours post-dose and a terminal half-life following intravenous dosing of 13 hours.

Pharmacokinetic and metabolism studies have been performed in mouse, rat, dog, and human after single and multiple administrations by oral and intravenous routes. The compound is moderately lipophilic (log D(7.4) 2.1) and basic (pK(a) 7.3). Maraviroc was incompletely absorbed in rat (approximately 20-30%) but well absorbed in dog (>70%). In mice AUC after oral administration was 3-fold higher than in control animals. In oral dose escalation studies in humans, the Maraviroc showed nonlinear pharmacokinetics, with increased dose-normalized exposure with increased dose size, consistent with saturation of P-glycoprotein. Metabolites were products of oxidative metabolism and showed a high degree of structural consistency across species under investigation .

Several pharmacological studies in humans have shown that that Maraviroc is metabolized primarily by CYP3A4 but that it does not inhibit or induce any of the P450 enzymes, that 5-15% of the dose is excreted unchanged in urine, that pharmacokinetics are similar between males and females, and that there is no significant difference in pharmacology between Asians and Caucasians .

Thus, Maraviroc may be used in all patient populations including those who are treated with inhibitors and inducers of CYP3A4. However, since Maraviroc is metabolized primarily by CYP3A4 and is P-gp substrate, dose adjustments are required when it is combined with potent CYP3A4 inhibitors or inducers. With potent CYP3A4 inhibitors, such as protease inhibitors (PIs) or ketoconazole, the dose of Maraviroc should be halved to 150 mg. This level of dose adjustment is also used for efavirenz when it is dosed with a booster dose of ritonavir.

With potent CYP3A4 inducers, such as efavirenz or rifampin, the dose of Maraviroc should be doubled to 600 mg. No dose adjustment is required when Maraviroc is dosed with renally excreted drugs, such as tenofovir or trimethoprim .

In a study of a pharmacokinetic-pharmacodynamic model clinical data from a first monotherapy study (study 1007) [57] was used to develop an optimal dose of Maraviroc. In a randomized, double-blind, placebo-controlled fashion 44 asymptomatic HIV-1-infected patients were enrolled. Patients received Maraviroc under food restrictions at 25 mg once daily or 50, 100, or 300 mg twice daily, or placebo for 10 days. Antiviral efficacy was assessed by measuring plasma HIV-1 RNA levels during screening, randomization, at baseline, and daily during the 10 days of treatment and at days 11 to 15, 19, 22, 25, and 40. Parameters derived from a viral dynamic model were used to calculate average viral inhibition fraction, decay rate of actively infected cells, and basic reproductive ratio for each treatment group. The decline rate in the 300 mg twice daily group was comparable to that induced by potent protease inhibitor monotherapy, but was significantly slower than that in patients receiving combination therapy including both protease inhibitor and reverse transcriptase inhibitors. The efficacy of inhibition *in vivo* was estimated to range from 0.15 to 0.38 for the 25 mg once daily dose group and from 0.88 to 0.96 for the 300 mg twice daily dose group. The model has aided the analysis and interpretation of the clinical data.

Summary

According to the results of the MOTIVATE trials, Maraviroc is of significant and high virological efficacy for patients with treatment experience and multiple

treatment failures. It shows superior virologic and immunologic efficacy compared to placebo regardless if combined with additional active drugs or without active drugs in OBT. In therapeutic dosing the side effects appear to be mild. Only headache, nausea and flatulence occurred slightly and not notably more frequently than in placebo control. There was no prolongation of QTc F and no increased hepatotoxicity reported. In study 1029, treatment of individuals with dualtropic or CXCR4-tropic HIV-1 infection with Maraviroc did not result in lowering HIV-RNA, but in a pronounced CD4 elevation.

Indeed Maraviroc therapy may induce tropism change by selection pressure. It is more likely however that CXCR-4 using variants emerge from a pre-existing reservoir then by coreceptor switch and circulating viruses revert to CRR5-tropic strains after cessation of therapy. It is still unclear today if coreceptor switch causes or if it is a result of disease acceleration. Further studies will be needed to investigate if coreceptor switch under Maraviroc therapy leads to disease progression. As of present knowledge, concerns about tropism change should not prevent Maraviroc use.

Several studies demonstrate that non-functional CCR5 may alter immune system response in M. tuberculosis, Listeria, West Nile Virus and Hepatitis B infection. At present, clinical use of Maraviroc is not associated with similar effects.

Maraviroc is metabolised by CYP3A4 but it does not inhibit or induce any of the P450 enzymes. The dosing of Maraviroc must be adjusted when co-administrated with potent inducers or inhibitors of CYP3A4.

Maraviroc is well tolerated, conveniently administered, does not alternate pharmacokinetics of co-administrated drugs and appears to have low long term toxicity. Its new mechanism of action might result in reducing the number of latently infected cells. On the basis of these characteristics Maraviroc is a promising candidate for first line therapy, especially because of the declining prevalence of CCR5-tropism in the course of HIV-1 infection. In the 1026 study however, slightly fewer therapy-naïve patients reached HIV RNA below 50 copies/ml when treated with Maraviroc plus ZDV/3TC compared to those patients treated with efavirenz plus ZDV/3TC. The 1026 study further stated that immunologic reconstitution was superior in Maraviroc arm and that fewer patients discontinued Maraviroc due to adverse events. The approval for first line therapy without further trials, eventually compromising also non-nucleoside backbones, subsequently remains uncertain.

Most of the results presented here are derived from studies which were performed in industrialized countries where subtype B is predominant and where up to 88% of viral isolates are CCR5-tropic during early time of infection. Dorr, Macartney et al. demonstrated that susceptibility to Maraviroc in R5 viruses does not depend on subtype. Viral isolates from different geographic regions do though differ in coreceptor usage. It has been widely accepted that HIV-1 subtype C has a high prevalence of exclusively CCR5-tropic strains even in the advanced stages of disease. Subtype E appears to be in possession of similar characteristics in coreceptor usage as sybtype B. Subtype D on the contrary appears to have a high prevalence of dualtropic and CXCR4 monotropic virus. Up to 50% of HIV-1 isolates with env subtype A were able to establish a productive infection by using the alternative coreceptors BOB/GPR15 and/or CXCR6 (Bonzo). While most HIV subtypes seem to show good response to Maraviroc, in patients with known infection by HIV subtypes A and D close clinical monitoring will be necessary and clinical efficacy should be studied in additional trials.

Reference List

1. Liu R, Paxton WA, Choe S et al. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. Cell 1996; 86(3):367-77.
2. Taylor JM, Wang Y, Ahdieh L et al. Causal pathways for CCR5 genotype and HIV progression. J. Acquir. Immune Defic. Syndr. 2000;23(2):160-171.
3. Berger EA, Murphy PM, Farber JM. Chemokine receptors as HIV-1 coreceptors: roles in viral entry, tropism, and disease. Annu.Rev.Immunol. 1999;17:657-700.
4. Doms RW. Unwelcome guests with master keys: how HIV enters cells and how it can be stopped. Top.HIV. Med. 2004;12(4):100-103.
5. Moore JP, Doms RW. The entry of entry inhibitors: a fusion of science and medicine. Proc.Natl.Acad.Sci.U.S.A 2003;100(19):10598-602.
6. Berger EA, Doms RW, Fenyo EM et al. A new classification for HIV-1. Nature 1998;391(6664):240.
7. Westby M, Whitcomb J Huang W. Reversible predominance of CXCR4 utilising variants in a non-responsive dual tropic patient receiving the CCR5 antagonist UK-427,857. Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections. 2004.
8. Richman DD, Wrin T, Little SJ, Petropoulos CJ. Rapid evolution of the neutralizing antibody response to HIV type 1 infection. Proc.Natl.Acad.Sci.U.S.A 2003;100(7): 4144-49.
9. Coakley E, Petropoulos CJ, Whitcomb JM. Assessing chemokine co-receptor usage in HIV. Curr Opin Infect Dis. 2005;18(1):9-15.
10. Petropoulos CJ, Parkin NT, Limoli KL et al. A novel phenotypic drug susceptibility assay for human immunodeficiency virus type 1. Antimicrob.Agents Chemother. 2000;44(4):920-928.
11. Labrosse B, Labernardiere JL, Dam E et al. Baseline susceptibility of primary human immunodeficiency virus type 1 to entry inhibitors. J.Virol. 2003;77(2):1610-1613.
12. Whitcomb JM, Huang W, Fransen S et al. Development and characterization of a novel single-cycle recombinant-virus assay to determine human immunodeficiency virus type 1 coreceptor tropism. Antimicrob.Agents Chemother. 2007;51(2):566-75.
13. Moyle GJ, Wildfire A, Mandalia S et al. Epidemiology and predictive factors for chemokine receptor use in HIV-1 infection. J.Infect.Dis. 2005;191(6):866-72.
14. Philpott SM. HIV-1 coreceptor usage, transmission, and disease progression. Curr.HIV.Res. 2003;1(2):217-27.
15. Wilkin TJ, Su Z, Kuritzkes DR et al. HIV type 1 chemokine coreceptor use among antiretroviral-experienced patients screened for a clinical trial of a CCR5 inhibitor: AIDS Clinical Trial Group A5211. Clin. Infect Dis. 2007;44(4):591-95.
16. Melby T, Despirito M, Demasi R, Heilek-Snyder G, Greenberg ML, Graham N. HIV-1 coreceptor use in triple-class treatment-experienced patients: baseline prevalence, correlates, and relationship to enfuvirtide response. J.Infect.Dis. 2006;194(2):238-46.

17. Poveda E, Briz V, de MC et al. Prevalence of X4 tropic HIV-1 variants in patients with differences in disease stage and exposure to antiretroviral therapy. J.Med.Virol. 2007;79(8):1040-1046.
18. Demarest, J. Abstract H-1136. ICAAC 2004. 2004.
19. Hunt PW, Harrigan PR, Huang W et al. Prevalence of CXCR4 tropism among antiretroviral-treated HIV-1-infected patients with detectable viremia. J.Infect.Dis. 2006;194(7):926-30.
20. Osmanov S, Pattou C, Walker N, Schwardlander B, Esparza J. Estimated global distribution and regional spread of HIV-1 genetic subtypes in the year 2000. J.Acquir.Immune.Defic.Syndr. 2002;29(2):184-90.
21. Casper C, Naver L, Clevestig P et al. Coreceptor change appears after immune deficiency is established in children infected with different HIV-1 subtypes. AIDS Res Hum Retroviruses 2002;18(5):343-52.
22. Tscherning C, Alaeus A, Fredriksson R et al. Differences in chemokine coreceptor usage between genetic subtypes of HIV-1. Virology 1998;241(2):181-88.
23. Abebe A, Demissie D, Goudsmit J et al. HIV-1 subtype C syncytium- and non-syncytium-inducing phenotypes and coreceptor usage among Ethiopian patients with AIDS. AIDS 1999;13(11):1305-11.
24. Cecilia D, Kulkarni SS, Tripathy SP, Gangakhedkar RR, Paranjape RS, Gadkari DA. Absence of coreceptor switch with disease progression in human immunodeficiency virus infections in India. Virology 2000;271(2):253-58.
25. Tien PC, Chiu T, Latif A et al. Primary subtype C HIV-1 infection in Harare, Zimbabwe. J Acquir Immune Defic Syndr. Hum Retrovirol. 1999;20(2):147-53.
26. van Rensburg EJ, Smith TL, Zeier M et al. Change in coreceptor usage of current South African HIV-1 subtype C primary isolates. AIDS 2002;16(18):2479-80.
27. Johnston ER, Zijenah LS, Mutetwa S, Kantor R, Kittinunvorakoon C, Katzenstein DA. High frequency of syncytium-inducing and CXCR4-tropic viruses among human immunodeficiency virus type 1 subtype C-infected patients receiving antiretroviral treatment. J.Virol. 2003; 77(13):7682-88.
28. Huang W, Eshleman SH, Toma J et al. Coreceptor tropism in human immunodeficiency virus type 1 subtype D: high prevalence of CXCR4 tropism and heterogeneous composition of viral populations. J.Virol. 2007; 81(15): 7885-93.
29. Kaleebu P, Nankya IL, Yirrell DL et al. Relation between chemokine receptor use, disease stage, and HIV-1 subtypes A and D: results from a rural Ugandan cohort. J.Acquir.Immune.Defic.Syndr. 2007;45(1):28-33.
30. Brown BK, Darden JM, Tovanabutra S et al. Biologic and genetic characterization of a panel of 60 human immunodeficiency virus type 1 isolates, representing clades A, B, C, D, CRF01_AE, and CRF02_AG, for the development and assessment of candidate vaccines. J.Virol.2005;79(10): 6089-101.
31. Menu E, Reynes JM, Muller-Trutwin MC et al. Predominance of CCR5-dependent HIV-1 subtype E isolates in Cambodia. J Acquir Immune Defic Syndr Hum Retrovirol. 1999;20(5):481-87.
32. Subbarao S, Vanichseni S, Hu DJ et al. Genetic characterization of incident HIV type 1 subtype E and B strains from a prospective cohort of injecting drug users in Bangkok, Thailand. AIDS Res.Hum.Retroviruses 2000; 16(8):699-707.
33. Cilliers T, Willey S, Sullivan WM et al. Use of alternate coreceptors on primary cells by two HIV-1 isolates. Virology 2005;339(1):136-44.
34. Bazan HA, Alkhatib G, Broder CC, Berger EA. Patterns of CCR5, CXCR4, and CCR3 usage by envelope glycoproteins from human immunodeficiency virus type 1 primary isolates. J.Virol. 1998;72(5):4485-91.
35. Zhang YJ, Dragic T, Cao Y et al. Use of coreceptors other than CCR5 by non-syncytium-inducing adult and pediatric isolates of human immunodeficiency virus type 1 is rare in vitro. J.Virol. 1998;72(11):9337-44.
36. Deng HK, Unutmaz D, KewalRamani VN, Littman DR. Expression cloning of new receptors used by simian and human immunodeficiency viruses.Nature1997;388 (6639): 296-300.
37. Begaud E, Feindirongai G, Versmisse P et al. Broad spectrum of coreceptor usage and rapid disease progression in HIV-1-infected individuals from Central African Republic. AIDS Res.Hum.Retroviruses 2003;19(7):551-60.
38. Pohlmann S, Krumbiegel M, Kirchhoff F. Coreceptor usage of BOB/GPR15 and Bonzo/STRL33 by primary isolates of human immunodeficiency virus type 1. J.Gen.Virol. 1999;80 (Pt 5):1241-51.
39. Tscherning-Casper C, Vodros D, Menu E et al. Coreceptor usage of HIV-1 isolates representing different genetic subtypes obtained from pregnant Cameroonian women. European Network for In Utero Transmission of HIV-1. J.Acquir.Immune.Defic.Syndr. 2000;24(1):1-9.
40. Zerhouni-Layachi B, Husain M, Ross MJ et al. Dual tropism of HIV-1 envelopes derived from renal tubular epithelial cells of patients with HIV-associated nephropathy. AIDS 2006;20(4):621-24.
41. Dorr P, Westby M, Dobbs S et al. Maraviroc (UK-427, 857), a potent, orally bioavailable, and selective small-molecule inhibitor of chemokine receptor CCR5 with broad-spectrum anti-human immunodeficiency virus type 1 activity. Antimicrob.Agents Chemother. 2005;49(11): 4721-32.
42. Mugwagwa T, Witten G. Coreceptor switching in HIV-1 subtype B and subtype C.Bull.Math.Biol.2007;69(1):55-75.
43. Pollakis G, Abebe A, Kliphuis A et al. Phenotypic and genotypic comparisons of. J.Virol. 2004;78(6):2841-52.
44. Fatkenheuer G, Pozniak AL, Johnson MA et al. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1. Nat.Med. 2005;11(11):1170-1172.
45. Saag, M. A multicenter, randomized, double-blind, comparative trial of a novel CCR5 antagonist, maraviroc versus efavirenz, both in combination with Combivir (zidovudine [ZDV]/lamivudine [3TC]), for the treatment of antiretroviral naive subjects infected with R5 HIV-1: week 48 results of the MERIT study. Abstract-4th IAS conference in Sydney. 2007.
46. Gulick, R. M. 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. Abstract-4th IAS conference. 2007.
47. van derRyst, E. 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. abstract,-4th IAS conference. 2007.
48. Mayer, H. 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 . Abstract THLB0215-4th IAS Conference. 2007.
49. McHale, M., Abel, S., and Russell, D. Overview of Phase 1 and 2a Safety and Efficacy Data of Maraviroc (UK-427, 857). 3rd IAS Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, Brazil, Abstract-TuOa0204. 2005.
50. Nelson, M. Efficacy and safety of maraviroc plus optimized background therapy in viremic, ART-experienced patients infected with CCR5-tropic HIV-1: 24-week results of phase 2b/3 studies. abstr 104aLB-14th Conference on Retroviruses and Opportunistic Infections. 2007.
51. Westby M, Lewis M, Whitcomb J et al. 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;80(10):4909-20.
52. Westby M, Smith-Burchnell C, Mori J et al. 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;81(5):2359-71.
53. Este JA, Telenti A. HIV entry inhibitors. Lancet 2007;370(9581):81-88.
54. Algood HM, Flynn JL. CCR5-deficient mice control Mycobacterium tuberculosis infection despite increased pulmonary lymphocytic infiltration. J.Immunol. 2004;173(5): 3287-96.
55. Glass WG, McDermott DH, Lim JK et al. CCR5 deficiency increases risk of symptomatic West Nile virus infection. J.Exp.Med. 2006;203(1):35-40.
56. Thio CL, Astemborski J, Bashirova A et al. Genetic protection against hepatitis B virus conferred by CCR5Delta32: Evidence that CCR5 contributes to viral persistence. J.Virol. 2007;81(2):441-45.
57. Rosario, M. C. A pharmacokinetic-pharmacodynamic model to optimize the phase IIa development program of maraviroc. J Acquir Immune Defic Syndr 42(2), 183-191. 2006.

Received: August 27, 2007 / Accepted: August 29, 2007

Address for correspondence:
Prof. Dr. Johannes R. Bogner
Department of Infectious Diseases
Med. Poliklinik
University Hospital of Munich, Campus Innenstadt
Pettenkoferstr. 8a

CURRICULUM VITAE

Matthias C. Mueller
Medical studies from 1998 to 2005 at the University of Freiburg, Germany, University of Salamanca, Spain and University of Buenos Aires, Argentina

Doctoral thesis with the topic: "Co-cultivation of endothelial cells and preadipocytes for generation of bioartificial, capillarised adipose tissue", in the Tissue Engineering Laboratory, University Hospital of Freiburg, Germany, in the years 2000 to 2005.

Since may 2006 medical doctor at the Department of Infectious Diseases, Medizinische Poliklinik, University Hospital of Munich, Campus Innenstadt; Germany

CURRICULUM VITAE

Johannes Bogner
Born in 1960, Johannes Bogner was educated in Munich. He received his Medical Education at the Munich University. During his training in Internal Medicine he was active in building up the Outpatient Clinic for Infectious Diseases. Additional Infectious Disease education was attained in Berlin, Germany and at the Albert Einstein Medical College in New York, USA. In 1993 he was appointed assistant professor and in 2001 he was awarded Professorship in Internal Medicine. At present he is Head of the Department of Infectious Diseases at the Munich University Hospital and lecturer at the Medical School.
At present he is chair of the scientific board of the German Infectious Disease Society (DGI).