HOW WILL CCR5 ANTAGONISTS INFLUENCE THE RECOMMENDATIONS FOR THE ANTIRETROVIRAL TREATMENT OF HIV-1 INFECTION

Jan van Lunzen

University Medical Centre Hamburg-Eppendorf and Heinrich-Pette-Institute for Experimental Virology and Immunology, Hamburg, Germany

Abstract

The new antiviral CCR5 antagonists have proven to be highly efficient in treatment experienced patient populations with multiple drug failure. Maraviroc is the most advanced compound in clinical development representing this new class of entry inhibitors. The favourable toxicity-, resistance- and pharmacokinetic profile of the drug has been proven in phase III trials in treatment naive and experienced patients. In the latter population, maraviroc had superior antiviral efficacy and immunological activity compared to OBT + placebo alone in the control group. The antiviral responses after 48 weeks were comparable to results obtained from phase III trials with raltegravir and other previous salvage regimens including, darunavir, tipranavir and enfuvirtide. Due to its unique mode of action with exclusive activity against CCR5 tropic strains, viral tropism testing will be mandatory before using CCR5 antagonists in the clinic. The corresponding tests are established and will be further validated. Results from clinical trials indicate that approximately half of the treatment experienced patients will predominantly harbour CCR5 tropic quasispecies and will thus qualify for treatment with CCR5 antagonists.

In treatment naïve patients maraviroc so far formally failed to prove its non-inferiority to a standard regimen consisting of AZT/3TC + efavirenz after 48 weeks. However, further 96 weeks data will be analysed from this study as well as antiviral efficacy in distinct patient subpopulations. Therefore, it is likely that maraviroc will be recommended in early stages of salvage therapy at present and might replace more inconvenient drugs like enfuvirtide in later lines of therapy. The drug class has also the potential to enter first line therapy but this has to be proven in future trials. Special patient populations like primary HIV infection (PHI), pre- and post exposure prophylaxis, co-infection with tuberculosis and hepatitis B may show special clinical benefit but this is also awaiting confirmation from prospective trials.

INTRODUCTION

At present different antiretroviral drugs are in development which interfere with the entry of HIV-1 into the host cell. Currently, the fusion inhibitory peptide enfuvirtide is the only licensed substance which acts at this very early time point of the viral replication cycle.

Other entry inhibitors are CCR5 antagonists, attachment inhibitors and monoclonal antibodies. Of those the CCR 5 antagonists maraviroc and vicriviroc are in later stages of clinical development and maraviroc has been approved for the treatment of HIV patients by the FDA. The potential impact of CCR5 antagonists on future treatment recommendations will be discussed in this review with a focus on maraviroc due to its recent licensing. Most of the notions concerning future treatment recommendations which are stated here are based on data from clinical trials with maraviroc and from the preclinical development program but remain purely speculative until final licensing and labelling has been performed by the responsible drug agencies. To facilitate an educated guess on the potential role of maraviroc in the treatment of HIV-1 infection certain properties of the drug and results from clinical trials will be highlighted in this article.

MODE OF ACTION AND PHASE I STUDIES

Maraviroc is a selective and slowly reversible CCR5 antagonist that has been shown to be active in vitro against a wide range of clinical isolates, including those resistant to existing drug classes. In healthy volunteers and asymptomatic HIV-1 infected patients, monotherapy with maraviroc, at doses up to 300 mg twice daily (BID) for up to 28 days, demonstrated a safety and tolerability profile that was not significantly different to placebo with a decrease of viral load of approximately 2 log₁₀ in HIV infected patients [6]. Pharmacokinetic studies suggested that both OD and BID dosing might be possible.

VIRAL TROPISM

Both pre-clinical selection experiments and exploratory in vitro studies conducted on pre- and post-treatment viruses from patients enrolled in the Phase 2a and Phase 2b/3 maraviroc clinical program have found that maraviroc acts as a highly selective and potent inhibitor of CCR5-tropic viruses. Thus an assay testing viral tropism (CCR5 versus CXCR4 co-receptor usage) will be mandatory before starting therapy with CCR5-antagonists [14]. Specific descriptions of the currently available genotypic and phenotypic tropism assays will be given at another section of this journal.
Results from clinical phase III trials showed that approximately half of the treatment experienced patient population screened in these trials harboured CCR5-tropic viral strains with an unknown percentage of minority quasispecies showing CXCR4-tropism [12]. A background change in tropism result from CCR5 to dual/mixed tropic between screening and baseline occurred in approximately 8% of patients. The clinical outcome in these patients was similar to that of patients with non-CCR5 tropic virus in one of these studies [21]. In patients with a CCR5 tropism result at screening/baseline who fail a maraviroc containing regimen, emergence of CXCR4-using virus was seen in the majority of cases. However, the clinical relevance of this finding remains to be elucidated since patients failing on a maraviroc containing regimen had a larger mean increase in CD4 from baseline compared to placebo, irrespective of tropism result at time of failure. There is no evidence to suggest that changes in tropism result which occur in the circulating virus from patients on maraviroc-containing regimens are caused by mutation of a CCR5-tropic virus to a CXCR4-using virus (i.e. no evidence of tropism switch) [18].

The presence of CCR5-tropic strains depends on the stage of the disease: in general it is observed that CCR5-tropic strains occur in less advanced stage of immunodeficiency and CXCR4-tropic strains will predominate in full blown AIDS with a mixed population immediately [21]. No easy to use surrogate marker for tropism switch does exist leaving phenotypic tests as the ultimate choice for assessment of co-receptor usage [20]. This would argue for the use of CCR5-antagonists in patient populations in less advanced stages of immunodeficiency with a high likelihood of the presence of CCR5-tropic strains predominating [13].

**Resistance**

Screening of large numbers of Env clones from baseline samples identified a low frequency of CXCR4-using clones that pre-existed maraviroc treatment and which were phylogenetically highly related to the on-treatment CXCR4-using virus. Further phylogenetic analyses suggested that emergence of a pre-treatment CXCR4-using virus (present at baseline but not detected) was by far the most likely explanation [18]. The pre-clinical studies of maraviroc resistance (with continued CCR5-tropism) were predictive of what was seen in the clinic. Dose response inhibition curves with plateaus in MPI are predictive of resistance to maraviroc, consistent with its mechanism of action as a non-competitive inhibitor of viral entry [3].

Preliminary sequence data of maraviroc-resistant viruses from 5 patients failing maraviroc containing regimens in the clinical program is consistent with the pre-clinical findings; namely that the V3 loop plays an important role in conferring resistance. In particular, an I26V mutation in the V3 loop may be a key mutation for some viruses, as may mutations that disturb the structure of the ‘GPG’ crown.

Site directed mutagenesis studies on viruses from 4 patients confirmed the importance of V3 loop mutations in conferring resistance to maraviroc. In all cases, specific mutations were necessary and/or sufficient to confer resistance. However, it is not possible to propose a genotypic (sequence) algorithm to identify maraviroc resistance. No consistent changes in amino acid sequence between different patients were associated with a maraviroc resistant phenotype [19]. Maraviroc resistant quasispecies are not cross-resistant to vicriviroc in all cases, some viral strains will retain sensitivity to the other CCR5-antagonist. Interestingly, the development of a resistant phenotype does not lead to a decrease in viral fitness, mutant viruses show the same replicative capacity compared to wild-type virus in vitro. Thus, the resistant phenotype is likely to persist after discontinuation of CCR5-antagonists. There is no evidence that failure on a maraviroc-containing regimen will lead to cross-resistance to enfuvirtide, and no rationale for cross-resistance between maraviroc and other drug classes. Similarly, viruses with reduced susceptibility to enfuvirtide were susceptible to maraviroc.

**Effects of Other Drugs on Maraviroc**

Since maraviroc will be applied exclusively in combination with other antiretroviral agents and a significant percentage of patients will receive other co-medications it is essential to know potential drug-drug interactions in order to foresee the position of maraviroc in different patient populations.

As maraviroc is a substrate for CYP3A4 and P-gp, its pharmacokinetics is likely to be affected by co-administration of inhibitors and inducers of these enzymes/transporters. In addition, in clinical practice, maraviroc will be co-administered with other antiretroviral drugs, many of which are known to affect CYP3A4 and/or P-gp activity. Hence, the main focus of the drug interaction studies has been to understand the impact of CYP3A4 and P-gp modulation in the complex dosing environment of OB/F to be used in Phase 2b/3 studies, with the aim of guiding dose adjustment recommendations for maraviroc. As maraviroc is also renally cleared (20.3% of total clearance), the effect of substrates and inhibitors of renal clearance (tenofoviro and co-trimoxazole) on the pharmacokinetics of maraviroc have also been investigated.

**Interactions with CYP3A4 Inhibitors**

Maraviroc pharmacokinetics in healthy volunteers were evaluated in combination with saquinavir ± ritonavir, Kaletra™, atazanavir ± ritonavir, tipranavir/ritonavir and ritonavir alone as a boosting dose. Ketoconazole was also studied as a reference CYP3A4 inhibitor. With the exception of tipranavir/ritonavir, which had no net effect, all other drugs caused an increase in maraviroc exposure with a range of AUC results increasing from 2.6 fold (ritonavir 100 mg BID) to 8.3-9.7 fold with saquinavir/ritonavir (2 studies). Thus once daily dosing of maraviroc in combination with boosted protease inhibitors seems to be a feasible option.
INTERACTIONS WITH CYP3A4 INDUCERS

Efavirenz and rifampicin are inducers of CYP3A4 and P-gp. The effect of both drugs on maraviroc pharmacokinetics was individually studied. They both reduced maraviroc exposure by 45% or more. Doubling the maraviroc dose restored exposure (AUC) to approximately 100%.

Because of the prevalence of tuberculosis in HIV-1 infected patients rifampicin is often a desirable component of an anti-tuberculosis regimen, however its enzyme inducing effects make some concomitant HIV-1 medications difficult to use and not recommended (e.g., efavirenz).

A simple doubling of maraviroc dosing corrects for the induction, therefore maraviroc may be particularly useful in HIV-1 patients co-infected with Mycobacterium tuberculosis. This makes twice daily dosing of maraviroc highly likely in both clinical scenarios described above.

SELECTION OF PATIENT POPULATIONS FOR TREATMENT EXPERIENCED STUDIES

Efficacy of maraviroc for the target indication, namely the management of treatment experienced patients infected with CCR5 tropic HIV-1, has been demonstrated in two independent, randomised, double-blind, placebo-controlled superiority studies. These studies were designed to reflect a heavily treatment-experienced HIV-1-infected population who were failing their current antiretroviral therapy or were infected with multi-drug resistant virus. Patients had at least 6 months of prior treatment with at least 1 agent (2 agents for PIs) from 3 of 4 antiretroviral drug classes and/or documented resistance to 3 of the 4 antiretroviral drug classes and plasma HIV-1 RNA ≥5000 copies/ml. Despite selecting patients with CCR5 tropic HIV-1 these 2 studies demonstrated similar baseline viral loads and CD4 cell counts to recent clinical studies of antiretroviral agents.

As in other salvage therapy trials patient randomization was balanced between the OBT and maraviroc groups. Moreover, the baseline characteristics of MOTIVATE 1 and 2 trials with maraviroc were strikingly comparable with patients enrolled in previous salvage trials like TORO 1 and 2, RESIST and POWER using other newly developed agents as the comparator. Baseline characteristics were also very similar to the patient population enrolled in the recently reported BENCHMRK 1 and 2 trials with raltegravir (Cooper D & Steigbigel R et al.: Abstract #105, CROI February 2007). This allows for some cross-study comparisons between the different trials although these data have to be viewed with caution.

PHASE III CLINICAL TRIALS IN TREATMENT EXPERIENCED PATIENTS

In two Phase 3 studies, MOTIVATE 1 and MOTIVATE 2, it has been demonstrated that a 300 mg dose equivalent of maraviroc, given once or twice daily, when dosed in combination with optimised background therapy (OBT) in treatment-experienced patients infected with CCR5 tropic HIV-1, leads to a greater and clinically relevant decline in viral load than OBT alone (placebo), with a mean reduction in HIV-1 RNA from baseline to Week 24 of at least 1.8 log\(_{10}\) copies/mL compared to approximately 1.0 log\(_{10}\) copies/mL with OBT alone. This translated to approximately a doubled likelihood to achieve a viral load less than 50 copies/mL in patients receiving maraviroc compared to placebo treated patients. This was achieved in about half of the total heavily treatment experienced patient population treated with maraviroc. In these studies enfuvirtide and tipranavir were available for the OBT, but not darunavir and ritonavir. Again it was shown that the substance performed best if combined with at least two other active drugs as judged by sensitivity scores. Especially the combination of maraviroc with enfuvirtide, in patients who were previously naive to it, yielded excellent virological responses.

The placebo response of >1.0 log\(_{10}\) copies/mL provides evidence that the OBT selections for these studies were appropriate, providing these patients with a clinically relevant reduction in HIV-1 RNA from baseline, which was comparable or greater than previous registrational trials for approved antiretroviral agents [2, 7, 9, 10]. The addition of maraviroc to this OBT, however, resulted in approximately 1.0 log\(_{10}\) copies/mL reduction in HIV-1 RNA above that of the placebo response. The greater efficacy provided by maraviroc compared with placebo in patients infected with CCR5 tropic HIV-1 was observed regardless of a patient's screening HIV-1 RNA level (<100,000 copies/mL or >100,000 copies/mL) or CD4 cell count at baseline. The dose adjustment implemented for patients receiving a PI (except for tipranavir/ritonavir) or delavirdine in their OBT was appropriate and did not adversely affect the efficacy outcome.

The mean change in CD4 cell count (cells/µl) was greater for the maraviroc treatment groups than placebo. The adjusted mean CD4 cell count increases observed in patients receiving maraviroc QD and BID were 108.6 cells/µl and 106.3 cells/µl, respectively, compared with placebo where an increase of 57.4 cells/µl was demonstrated. Maraviroc administration in patients infected with dual/mixed tropic or CXC4-using HIV-1, or in patients whose virus was non-phenotypable, did not result in adverse effects on viral load or CD4 count.

There was no indication of a clinically meaningful difference between maraviroc QD and BID across the whole population studied, based on the primary and key secondary efficacy endpoints measured following 24 weeks of therapy. However, certain subgroups, notably patients with lower CD4 count, higher viral loads and fewer potentially active drugs in their OBT, seem to receive greater benefit from maraviroc BID. These studies also demonstrated an acceptable safety and tolerability profile with no significant effect on QTc interval nor an increase in the incidence of hepatotoxicity, infections or malignancies, relative to placebo. Nasopharyngitis and bronchitis were the most common side effects which were thought to be related to maraviroc treatment. No other infections were reported more often for maraviroc compared to placebo. The maraviroc treatment arms also showed a favourable lipid profile.
The clinical development of another CCR5 antagonist, vicriviroc, is not that advanced yet. Here, data from a phase II dose finding study in treatment experienced patients indicate an overall good antiviral efficacy of the 10mg and 15mg dose groups. In these patients viral load dropped by 2 log_{10} after 48 weeks which was superior to the placebo + OBT control arm [8]. Moreover, the development of vicriviroc was delayed by some safety issues in the past which did not appear to be of clinical significance in the above mentioned phase II trial but these data need further confirmation from ongoing studies with larger patient numbers.

**Phase III Clinical Trials in Treatment Naïve Patients**

Recently the preliminary 48 week results of a phase III clinical trial (MERIT) comparing maraviroc 600 mg QD vs. 300 mg BID vs. efavirenz all combined with AZT and 3TC as the nucleoside backbone were presented. The QD arm was prematurely stopped due to inferior efficacy. The statistical design of the study was a non-inferiority trial with a confidence interval not worse than 10% compared to the control group (in previous trials 12.5%). There was no difference between the groups concerning the primary endpoint of a viral load reduction to <400 RNA copies/ml after 48 weeks. For the endpoint <50 RNA copies/ml, however, maraviroc failed to show statistical non-inferiority in this statistical analysis. The difference was modest in the intent to treat analysis with 69.3% of patients achieving this viral load reduction in the efavirenz arm compared to 65.3% in the maraviroc BID group [15]. The trial is extended to 96 weeks and further analyses are ongoing. The increase of CD4 counts at week 48 from baseline was better in the maraviroc group (169 cells/µl vs. 142 cells/µl) which is consistent with the results obtained in treatment experienced patients showing favourable CD4 responses in the maraviroc groups. This phenomenon which already occurs very early after initiation of maraviroc therapy may be at least partially explained by a redistribution of T helper cells to the periphery by blocking CCR5 receptors on CD4+ T cells which serve as a homing receptor to lymphatic tissues. Another interesting finding was a striking difference in a post hoc analysis of these data comparing recruiting centres from northern and southern hemisphere. Here non-inferiority was shown for maraviroc in the northern hemisphere but not in the south [15]. The underlying reason for this remains to be elucidated. Possible explanations include different geographical distribution of viral tropism, centre effects, less tolerability in non-white populations or merely a random effect.

Maraviroc was again well tolerated in this study with no different side effects than previously observed in treatment experienced populations. Only minor effects on lipid metabolism were observed in the maraviroc arm underlining the favourable toxicity profile of the drug.

In summary, at present maraviroc failed to demonstrate non-inferiority to efavirenz after 48 weeks in this trial. However, statistical differences were small and further analyses are awaited as well as 96 week data from the extension phase of this study. Hence, licensing of maraviroc in 2007 is limited to treatment experienced patients.

**Special Patient Populations**

Due to its specific mode of action, CCR5 antagonists might be of special interest in distinct patient subpopulations and clinical settings. Since new HIV infections occur almost exclusively after inoculation and dissemination of CCR5 tropic viral strains [23], CCR5 antagonists might be of special use in primary HIV infection (PHI). At this earliest stage of the disease nearly all virus offspring is generated by the replication of CCR5 tropic variants, although CXCR4 using viruses may also be transmitted but do not replicate efficiently at this point of time [1, 16]. Hence treatment of PHI with CCR5 antagonists might be beneficial even without prior testing of viral tropism. The same arguments warrant further investigation of CCR5 antagonists as pre- or post exposure prophylaxis (PrEP and PEP). If these theoretical considerations might translate into a clinical benefit needs to be studied in future clinical trials.

The favourable pharmacokinetic profile of maraviroc when given in combination with inducers of the CYP3A4 system makes it a very attractive antiretroviral agent in patients who are receiving concomitant anti-tuberculosis combination therapy. In these patients who receive rifampicin in the vast majority of cases, a simple doubling of the daily maraviroc dose might correct for the decrease of plasma levels caused by the CYP3A4 induction by rifampicin. This is potentially of great benefit for patient populations in less developed countries with a high burden of HIV/Tb co-infection.

Another co-infection might be of interest when discussing the indication for the use of CCR5 antagonists, namely co-infection with hepatitis B. Data from a recently published study indicate that genetic polymorphisms of the CCR5 receptor are associated with less viral persistence in HBV infection [17]. Of note, naturally acquired HBV infection failed to establish chronic disease in nearly all subjects who were homozygous for the delta32-deletion of the CCR5 receptor and those who were heterozygous for this allele still had a better clinical outcome indicating that CCR5 contributes to viral persistence in HBV infection. This was also true for patients who were co-infected with HIV. As a consequence one might speculate that CCR5 antagonists might be of special interest in the treatment of patients with HIV/HBV co-infection, but this has to be proven by future clinical studies in this distinct patient population which is of growing interest worldwide.

**Conclusions on the Influence of CCR5 Antagonists on Treatment Recommendations**

The above mentioned facts and speculations argue for the use of maraviroc and potentially other future CCR5 antagonists (vicriviroc) in treatment experi-
enced patients first. In these patient populations both drugs have shown high efficacy which is superior to OBT + placebo alone, although existing clinical data are more elaborated for maraviroc so far due to its later stage in clinical development. Therapy with maraviroc should possibly not be delayed until very advanced stages of immunodeficiency are established since a high proportion of these patients will predominantly harbour dual or CCR4 tropic variants [1]. The clinical benefit of maraviroc was proven in patients with failure of therapy to multiple classes of antiretrovirals (up to three) with proven CCR5 tropism of circulating viruses. Thus future guidelines will recommend the use of maraviroc in third or later lines of therapy after testing of viral tropism. As a consequence tropism assays will be mandatory prior to therapy and their availability and validity will have a large impact on the clinical use of the compound [11]. Maraviroc has the potential to be recommended even in earlier lines of therapy in experienced patients due to its unique mode of action, its lack of cross-resistance with other antiretroviral agents and its favourable toxicity and pharmacokinetic profile. It may be recommended for second line therapy of patients with resistance or intolerability to NNRTI or boosted PI regimens after initial treatment failure. Future studies will be needed to define the role of maraviroc in this setting and if it is superior to the current treatment strategies after first time failure. The potential for once daily dosing and a good safety profile makes this approach very likely.

In later lines of therapy failure, maraviroc has already proven its superiority over standard salvage therapies. Here the overall assessment shows comparable benefit for maraviroc and raltegravir. Both drugs have proven to lead to sustained reduction of viral load to below the limit of detection in a high proportion of patients which is comparable to earlier salvage trials with darunavir (POWER), tipranavir (RESIST) and enfuvirtide (TORO) [2, 7, 9, 10]. The combination of both drugs will be highly interesting in this context in order to even increase the percentage of patients with complete control of viral replication to an extent which is observed in treatment naive patients. Both drugs may be recommended in treatment experienced patients with multiple drug failure due to resistance or intolerability in combination with two other active drugs. Whether it will be advisable to use maraviroc or raltegravir first, or one or the other even prior to second generation PI’s (darunavir, tipranavir) remains to be elucidated. Certainly there is a great potential for maraviroc to enter these earlier stages of salvage therapy. In later stages of salvage therapy maraviroc will have an influence on the use of enfuvirtide in patients with the option of two other active drugs remaining. Here enfuvirtide use will be delayed until maraviroc based regimens will fail. Moreover, in deeper salvage situations maraviroc can be very efficiently combined with enfuvirtide enhancing the potential armamentarium in late stage disease. The combination with integrase inhibitors will be also of special interest in this setting and might even further delay enfuvirtide use.

For the moment it is very likely that maraviroc use will be restricted to treatment experienced patients since the drug formally failed to document that it is non-inferior to combivir + efavirenz after 48 weeks [15]. However, the differences between the groups were small and further statistical analyses are awaited later this year. It will be of special interest to analyse the difference between the results obtained from northern compared to the southern hemisphere and from distinct subgroups (e.g. high viral loads, low CD4 counts at study entry). This study will be extended to 96 weeks and might again change the recommendations including the treatment of antiretroviral naive patients with maraviroc in the future, in case those non-inferiority criteria are met at this time. In terms of tolerability, pharmacokinetics and convenience maraviroc clearly has the potential to be used in treatment naive patients in the near future. Moreover, special patient populations like co-infection with tuberculosis and hepatitis B may show the greatest clinical benefit from treatment with maraviroc due to the data discussed above. Finally, the clear predominance of CCR5 tropic strains in newly transmitted infections render CCR5 antagonists to be the drug of choice for pre- and post-exposure prophylaxis which has to be proven in prospective clinical trials [4, 5, 23].

REFERENCES

12. Moore JP, Kitchen S, Pugach P et al. The CCR5 and CXCR4 coreceptors - central to understanding the trans-
mission and pathogenesis of the human immunodeficien-
cy virus type 1 infection. AIDS Res Human Retrovir
13. Moyle GJ, Wildfire A, Mandalia S et al. Epidemiology and
predictive factors for chemokine receptor use in HIV-1
phenotypic drug susceptibility assay for human immuno-
deficiency virus type 1. Antimicrob Agents Chemother
double-blind, comparative trial of a novel CCR5 antago-
nist, 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. 4th
IAS Conference 2007, Abstract no. WESS104
viral evolutionary changes associated with the progression
of human immunodeficiency virus type 1 infection. J Virol
17. Thio CL, Astemborski J, Bashirova A, Mosbruger T,
Greer S, Witt MD, Goedert JJ, Hilgartner M, Majeske A,
O’Brien S, Thomas DL, Carrington M. Genetic protec-
tion against hepatitis B virus conferred by CCR5delta32:
Evidence that CCR5 contributes to viral persistence. J Vi-
18. 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 Vi-
maximal inhibition in phenotypic susceptibility assays indi-
cates that viral strains resistant to the CCR5 antagonist
maraviroc utilize inhibitor-bound receptor for entry. J Vi-
20. 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 co-receptor tropism. Antimicrob Agents Chemother
2007;51:566-75.
21. Wilkin TJ, Su Z, Kuritzkes DR et al. HIV type 1
chemokine receptor use among antiretroviral-experienced
patients screened for a clinical trial of a CCR5 inhibitor:
AIDS Clinical Trial Group A5211. Clin Infect Dis 2007;
44:591-5.
22. Wyatt R, Kwong PD, Desjardins E, Sweet RW et al. The
antigenic structure of the HIV gp120 envelope glyco-
characterization of HIV-1 patients with primary infection.

Received: August 27, 2007 / Accepted: August 28, 2007

Address for correspondence:
Jan van Lunzen, M.D. PhD
Associate Professor of Medicine
Medical Director
University Medical Centre Hamburg-Eppendorf
Infectious Diseases Unit
Martinistrasse 52
20251 Hamburg
Germany
Tel.: +49-40/42803-2831
Fax: +49-40/42803-5187
Email: v.lunzen@uke.uni-hamburg.de

Curriculum Vitae

Jan van Lunzen

Jan van Lunzen currently serves as the Medical Director of the Infectious Dis-
cases Unit at the University Medical Centre Hamburg-Eppendorf, Germany.
He is also head of the HIV Clinical Trial Unit at the same institution and the
HIV Immunology Research Laboratory at the Heinrich-Pette-Institute for
Experimental Virology and Immunology at the University of Hamburg.
He received his training in internal medicine at the Bernhard-Nocht-Institute
for Tropical Medicine and the University Medical Centre Eppendorf in
Hamburg, Germany. He is consultant for Internal Medicine and Infectious
Diseases and holds a diploma in Tropical Medicine and Parasitology. Since
2004 he is adjunct Professor of Medicine at the University of Hamburg. He
is involved in patient care since 1987 and acted as principal investigator in
numerous trials on treatment of HIV infection and opportunistic diseases.
He is also interested in basic and translational research focussed on the role
of the lymphatic tissue, follicular dendritic cells and immune activation for
HIV pathogenesis. He is author of numerous scientific articles on these top-
ics which have been published in peer reviewed journals. For this work he
was awarded with the German AIDS Research Prize and the Meta-Alexander
Award of the German Society of Infectious Diseases. He serves as an exter-
nal advisor to the French AIDS Research Agency (ANRS) since 2002 and to
the Commission for Somatic Gene Therapy in Germany.