National PBM Drug Monograph

Emtricitabine (Emtriva®)

VHA Pharmacy Benefits Management Strategic Healthcare Group
and the Medical Advisory Panel
July 2003

Executive Summary:

A 1-2 page executive summary should accompany each monograph or class review. The summary should consist of point-by-point highlights that are critical for decision-making. Please refer to the executive summaries that are part of the MAP guidelines for examples. These can be located at http://vaww.pbm.med.va.gov **under Treatment Guidelines.**

Introduction

Emtricitabine was approved on July 2, 2003 for use in combination with other antiretrovirals (ARVs) to treat HIV-1 infection in adults. This indication was based upon virologic (HIV viral load) and immunologic (CD4 lymphocyte count) responses during controlled clinical trials in ARV-naïve and ARV-experienced patients. To date, only one of these clinical trials has been published in a peer-reviewed journal while the others have been presented at scientific meetings in oral presentations and poster formats. Information presented in this monograph includes much of this information as well as data filed with the FDA for the new drug application (NDA).

Emtricitabine belongs to the nucleoside reverse transcriptase inhibitor (nRTI) class of anti-HIV agents. There are currently 9 products from the nRTI class of anti-HIV agents on the VA National Formulary. Each has a unique profile that permits its use in a specific patient relative to co-administered medications, existing resistance mutations and co-morbid conditions. For this review, all drugs in the nRTI class will be included to permit comparisons where data are available. The medications are:

Single Agent	Co-formulated Product
abacavir (ZIAGEN®, **ABC**)	lamivudine/zidovudine (Combivir®, **CBV**)
didanosine (VIDEX®, VIDEX® EC, **ddI**)	abacavir/lamivudine/zidovudine (Trizivir®, **TZV**)
lamivudine (EPIVIR®, **3TC**)	
stavudine (ZERIT®, ZERIT® XR, **d4T**)	
tenofovir (VIREAD®, **TFV**)	
zalcitabine (HIVID®, **ddC**)	
zidovudine (RETROVIR®, **ZDV**)	
*emtricitabine (Emtriva™, **FTC**)**	

*under review with this submission, **bold** indicates common abbreviation

The time span since the first FDA approved agent, zidovudine, to date covers 16 years. The first four agents to be approved were evaluated as monotherapy employing disease progression and/or time to death as markers of efficacy. In 1995, with the approval of lamivudine, there was a shift to dual nRTI therapy and in 1996 following the approval of protease inhibitors (PI), the current model of 3 or more drugs in an ARV regimen using multiple classes of agents was born. Studies demonstrating the association between surrogate markers of disease (CD4+ lymphocyte counts and HIV plasma viral RNA levels) and disease progression were published and another shift in care, to measuring markers of disease progression, changed clinical trials design and clinical care. This rapidly changing clinical management model dramatically impacted care while creating confusion on how to interpret extrapolated efficacy and toxicity data from earlier mono and dual therapy clinical trials.

Current drug development trials only study a single agent as monotherapy for a short period of time (2 weeks) to limit the possible development of resistance in that study cohort. As a result, there is practically no information on the long-term effect (clinical outcome or toxicity related) of any single agent approved since 1996. Also, ARVs are to be prescribed as a multidrug regimen making assessment of toxicities difficult especially when agents share common side effect profiles (e.g. rash).

Pharmacology/Pharmacokinetics

The nRTI class of anti-HIV agents function by inhibiting the HIV reverse transcriptase enzyme through competition with the host's natural intracellular nucleotide pool. If incorporated into the subsequent viral DNA, each of these agents leads to chain elongation termination. Seven of the agents are nucleoside analogues while one, tenofovir, is a *nucleotide* in product form. The nucleosides to which these agents can substitute for are listed in the table below.

Nucleoside	nRTI inhibitor
Adenosine	didanosine, tenofovir
Guanosine	abacavir
Cytidine	emtricitabine, lamivudine, zalcitabine
Thymidine	stavudine, zidovudine

Since many of these compounds compete within the same nucleotide pool, antagonistic, additive, or synergistic intracellular actions may exits. Data collected *in vitro* or *in vivo* regarding potential intracellular interactions are limited for the earlier approved medications and the results vary greatly by the type of cell line studied and *in vitro* model. Data suggest that zidovudine does decrease phosphorylation of stavudine and therefore co-administration of these two medications is not recommended. Other *in vitro* studies have shown that ribavirin and doxorubicin also decrease phosphorylation of stavudine and that those combinations should be avoided.

Pharmacokinetic parameters are presented below for emtricitabine as well as the other nRTI class agents. Data for co-formulated products (lamivudine/zidovudine (Combivir®) and abacavir/lamivudine/zidovudine (Trizivir®)) and for the extended release products (didanosine (Videx®EC) and stavudine (Zerit®XR)) should refer to parent compound listed below.

	FTC*	**ABC**	**ddI**	**3TC**	**d4T**	**TFV**	**ddC**	**ZDV**
Bioavailability (%)	93	83	33 - 43	86	86	25	> 80	64
Plasma half-life (hr)	10	1.5	1.3 - 1.6	5 - 7	1.5	12 - 14	2	0.5 - 3
Intracellular half-life (hr)	39	3.3	25 - 40	12	3.5	10 - 50	3	3
Protein Binding (%)	< 4	50	< 5	< 36	Negligible	< 7.2	< 4	< 38
Metabolism**	OX GLUC	AD GT	Renal 50%	Renal	Renal 50%	Renal	Renal 70%	GLUC

** OX – oxidation, GLUC - glucuronidation, AD – Alcohol dehydrogenase, GT – glucuronyl transferase

Clinical trials for the earlier agents used the plasma half-life to determine dosing intervals. With improved technology to measure the intracellular nucleotide pool, dosing intervals have been changed to reflect that pharmacokinetic parameter. As example, the dosing interval for zidovudine when first approved was 200mg every four hours (around the clock) based upon a plasma half-life as low as 0.5 hours. With an intracellular half-life of 3 hours, zidovudine was studied at TID and BID dosing schedules and today is dosed twice daily. Clinical trials using surrogate markers have confirmed that it is appropriate to use the intracellular half-life for all the nRTI class agents in determining dosing intervals.

Virology – Drug Resistance

Emtricitabine-resistant isolates of HIV-1 have been isolated from *in vitro* experiments and though genotypic testing has shown a mutation at codon 184 (M184V/I). A mutation at codon 184 of the HIV reverse transcriptase (RT) gene is the common change associated with *in vitro* and *in vivo* resistance to lamivudine (M184V). In clinical trials, emtricitabine-resistant isolates have been recovered with 38% of isolates from virologic failures in drug naïve subjects showing decreased susceptibility to emtricitabine. Genotype analysis of these patient isolates showed M184V/I mutations in the RT gene. This information suggests that emtricitabine may have limited use in a patient who already has a M184V/I mutation, as in the case of past exposure and resistance to lamivudine. In addition, patients treated first with emtricitabine who develop a M184V mutation in the RT gene will likely not benefit from lamivudine therapy. However, stavudine, tenofovir, and zidovudine susceptibilities are enhanced by the presence of a M184V mutation and therefore it may be appropriate to continue emtricitabine or lamivudine to benefit other medications in the regimen.

A full discussion of drug resistance, including a discussion of which drugs to potentially use first or last in a given patient, is beyond the scope of this drug monograph. For future information, the reader can find complete information about HIV resistance testing at www.hivresistanceweb.com.

FDA Approved Indication(s) and Off-label Uses

> "Emtricitabine is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in adults. This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts from controlled studies of 48 weeks duration in antiretroviral naïve and antiretroviral-treatment-experienced patients who were virologically suppressed on an HIV treatment regimen. In antiretroviral-treatment-experienced patients, the use of emtricitabine may be considered for adults with HIV strains that are expected to be susceptible to emtricitabine as assessed by genotypic or phenotypic testing."

This indication covers the entire spectrum of care for HIV infected patients. Emtricitabine has not been studied in the settings of post-exposure prophylaxis or in acute HIV seroconversion.

Current VA National Formulary Status

There are currently 9 medications, including the coformulated products, on the VA National formulary in the nRTI class for the treatment of HIV infection. These medications are classified as anti-infectives, where restrictions on use may be placed at VISN and/or local facility levels. Emtricitabine is currently a non-formulary item being reviewed for formulary addition.

Dosage and Administration

The adult dose established from clinical trials for emtricitabine is 200mg orally once-daily with or without food. A summary covering key administration information for the nRTI class is listed below. The asterisk indicates that the drug has been approved for the listed schedules however the least frequent number of doses per day is preferred. The current Department of Health and Human Services (DHHS) guidelines for the treatment of HIV infection recommend at least two of the drugs within the nRTI class be used as part of a ARV regimen. The table above shows that a number of "QD" nRTI "backbone" regimens can be assembled.

Drug	# Pill per dose	Schedule	Renal Dosing*	Diet restrictions
abacavir	1	BID	unknown	none
didanosine[!]	1	QD, Q12H	< 60 ml/min	empty stomach
emtricitabine	1	QD	< 50 ml/min	none
lamivudine	1	QD, BID	< 50 ml/min	none
stavudine[!]	1	QD, Q12H	< 50 ml/min	none
tenofovir	1	QD	unknown	with food
zalcitabine	1	Q8H	< 40 ml/min	none
zidovudine	1	BID, TID	< 15 ml/min	none

*Renal dosing indicates when the standard adult dose/schedule should be modified to match some level of renal insufficiency. Unknown – no studies have been performed in this population. [!] Dose should be decreased in patients < 60 kg.

Little pharmacokinetic information is available regarding dosing these agents in patients with various degrees of hepatic insufficiency. Of note these medications are primarily renally cleared, likely making mild hepatic insufficiency less of an issue or contraindication..

Efficacy Measures

Caution needs to be used when interpreting and extrapolating information collected in randomized, prospective clinical trials using HIV treatment regimens into the real world. The areas key to understanding the generalizability of the information include;

1) Patient demographics – Age, Race, Sex
2) Geographic location (USA, Europe, Africa, etc) – different viral clades and potential for drug resistant reservoir where history of heavy ARV exposure in the region (e.g. US *vs* Africa)
3) General study design – ability to placebo control (e.g. pill burden), fair comparison of dosing schedule(QD *versus* q8h), switching out or adding to current regimen
4) Known toxicity profiles of other co-administered ARVs
5) Drug treatment history – naïve to therapy or experienced (and if so to what agents or class of agents)
6) Baseline clinical HIV status – Clinical AIDS diagnosis, entry CD4+ lymphocyte count and HIV viral load, stratification by range (e.g. HIV viral load > 100,000 copies/ml)
7) Comorbid disease burden – co-infected with hepatitis B/C, other chronic disease (cardiovascular, endocrine, Mental Health Disease, etc)
8) History of or active substance use and abuse (illicit or prescriptive) including alcohol
9) Concomitant medications – what was excluded from use in clinical trials
10) Study Duration – current FDA requirements are for a minimum of 48 weeks although historic data are at 24 weeks
11) Outcomes analysis – Intent-to-treat (various models) vs. On-treatment

Taking into consideration these factors, the clinical trials available for review on the clinical efficacy of emtricitabine have the following general characteristics.

Drug Naïve Population

a) ANRS **091** – Open label trial in forty (n=40) subjects of emtricitabine, didanosine, and efavirenz in a once daily regimen. Inclusion : CD4 > 100 cells/mm^3 and HIV-1 viral load > 5,000 copies/ml plasma. Duration: 24 months (24 week published data presented) Location: Europe
b) Gilead **301** – randomized, double blind placebo controlled (n=571, 1:1 per study arm) trial of stavudine/didanosine/efavirenz *versus* emtricitabine/didanosine/efavirenz. Stavudine was dosed BID with all other agents dosed QD. Inclusion: No CD4 limits, HIV-1 RNA stratification by >/< 100,000 copies/ml. Duration: 48 weeks Location: North America, South America, Europe

Drug Experienced Population

a) ANRS **099** (Alize) – Randomized open-label, multicenter switching trial (n=355, 1:1 per arm). Subjects stable on a protease inhibitor (PI) plus two nRTIs randomized to remain on their regimen or switch to emtricitabine/didanosine/efavirenz (switching at least 2 drugs). Inclusion: no prior ddI monotherapy, nonnucleoside reverse transcriptase inhibitor (nnRTI class, e.g. efavirenz) naïve, CD4 ≥ 100 cells/mm^3, and HIV-1 RNA < 400 copies/ml *for at least 6 months*. Duration: 48 weeks. Location: France

b) Gilead **303** - Randomized open label, multicenter trial switching lamivudine for emtricitabine in patients stable on lamivudine + (stavudine or zidovudine) + (nnRTI or PI) (n=440, 2:1 switch). Inclusion: no CD4 limits, HIV-1 RNA < 400 with stratification by < 50 and 50-400 copies/ml). Duration: 48 weeks. Location: France

Clinical Trials Data

Drug Naïve Studies

	Study		
	ANRS 091*	**Gilead 301**	
Regimen	FTC + ddI + EFV	**FTC** + ddI + EFV	d4T + ddI + EFV
Schedule	all QD	all QD	d4T BID, others QD
Sample (n)	40	286	285
Duration	24 weeks	48 weeks	
Analysis Type	ITT	ITT	
Age (mean, years)	33	36	36
Sex (% male)	88	84	86
Race	not reported	Combined: 52% White, 16% Black, 26% Hispanic	
Baseline Labs			
CD4 # (mean)	373	312	324
HIV RNA (copies/ml)	58,884	69,096	69,096
HIV RNA > 100,000 (%)	not reported	41	40
Endpoint Labs	Week 24	Week 48	
CD4 change	+ 159	+ 168	+ 134 (p<0.05)
HIV RNA (< 400)	98%	80%	67% (p= 0.001)
HIV RNA (< 50)	98%	74%	58% (p=0.0001)

*additional data have been presented out to 2 years on this cohort. The data presented here are from the Molina et.at. *JID* 2000. ANRS 091 was not used by the FDA for inclusion in the package insert as it is not a Phase III comparative trial.

In drug naïve subjects the single double blind, placebo controlled trial (Gilead 301) demonstrated that subjects receiving emtricitabine, didanosine and efavirenz were more likely to have an HIV viral load of < 400 or < 50 copies/ml after 48 weeks, compared to those who received stavudine, didanosine and efavirenz. It is important to note that the comparison prescribed stavudine every twelve hours, the FDA approved schedule at the time this clinical trial was completed. Currently, stavudine extended release formulation is approved for use once-daily.

Drug Experienced Studies – Both therapeutic switches in patients on stable regimens

	Study			
	ANRS 099*		**Gilead 303**	
Regimen	stable on 2 nRTI + PI		3TC + (d4T or ZDV) + (PI or nnRTI)	
Randomized to	same	FTC + ddI + EFV	same	switch FTC for 3TC
Schedule	various	QD	various	various
Sample (n)	177	178	146	294

Duration	48 weeks		48 weeks	
Analysis Type	ITT		ITT	
Age (mean, years)	41	41	43	42
Sex (% male)	86	85	87	85
Race	60% white 21% black 13% hispanic	66% white 21% black 13% hispanic	60% white 21% black 13% hispanic	60% white 21% black 13% hispanic
Baseline Labs				
CD4 #	547	519	533	524
HIV RNA (copies/ml)	all subjects < 400		all subjects < 400	
Endpoint Labs				
Virologic rebound (>400)	10%	12%	8%	7%

*Molina JM et al 10th CROI Boston, 2003, Poster #551

Both of these clinical trials involved changing a drug regimen in a patient population with a healthy CD4 lymphocyte count and an undetectable HIV viral load. These data do not provide any information regarding the use of emtricitabine as a second line agent after virologic failure of the initial dual nRTI containing regimen. This is especially important given the extensive historical use of lamivudine in the VA population.

Adverse Effects (Safety Data)

Toxicities and adverse reactions/events for HIV related medications can be classified into acute and those due to chronic exposure. Many of the acute reactions are limited in scope with many patients and providers deciding to continue therapy and manage these side effects with OTC and/or prescription products. Each HIV medication is studied as part of a regimen and there is little, short-term exposure information on monotherapy for drugs approved after 1995. The current FDA model for HIV clinical trials design is to evaluate an investigational agent in ARV drug naïve and ARV drug experienced populations for at least 48 weeks duration. Depending on pill burden and known side effect profiles of the other agents used in the regimen, the study may or may not be truly placebo controlled.

This monograph provides comparisons within the nRTI class where appropriate. Trying to compare toxicity data is difficult as the other agents in a particular ARV regimen may contribute; the bulk of the toxicity or toxicities reported may be enhanced in the presence of one or more other medications. Finally, it is difficult to extrapolate the rates of drug toxicities from early (mono or dual therapy) clinical trials as dosages and the severity of disease in the patient population have changed over time. Therefore, for the purposes of this review, the toxicities presented in the clinical trials for emtricitabine are presented followed by a summary table of data published for each of the medications in the nRTI class.

The table below lists the toxicity data, subjective and objective, seen during the two registry trials for emtricitabine.

Drug Naïve Population

	Gilead 301	
Randomized to	d4T + ddI + EFV	**FTC** + ddI + EFV
Subjects (n)	285	286
Study Discontinuation	78 (27%)	49 (17%)
Adverse event	33 (12%)	16 (6%)
Treatment failure	22 (8%)	8 (3%)
Other	25 (9%)	25 (9%)

Significant AEs **(p < 0.05)***		
Diarrhea	**32%**	23%
Nausea	**23%**	13%
Abnormal dreams	**19%**	11%
Neuropathy/peripheral neuritis	**13%**	4%
Parethesias	**12%**	6%
Increased cough	8%	**14%**
Skin discoloration	0.4%	**3.5%**
Laboratory abnormality		
Serum amylase (>2 xs UNL)	**10%**	5%

*__bold__ indicates where significantly (p<0.05) higher rates of events occurred
Skin hyperpigmentation, isolated to the soles and palms, was more prevalent in black (13.5%) and Hispanic (2.6%) patients than caucasian (0.7%).

Drug Experienced Studies – Both therapeutic switches in patients on stable regimens

	Study			
	ANRS 099		**Gilead 303**	
Regimen	stable on 2 nRTI + PI		3TC + (d4T or ZDV) + (PI or nnRTI)	
Randomized to	same	**FTC** + ddI + EFV	same	switch **FTC** for 3TC
Subjects (n)	177	178	146	294
Study Discontinuation	26 (15%)	23 (13%)	10%	15 %
Adverse event	18 (10%)	12 (7%)	0	4%
Virologic failure	1 (<1%)	5 (3%)	10%	12%
Other	6 (3%)	6 (3%)	0	0
Death	1 (<1%)	0		
Significant AEs (p < 0.05)				
Headache	Data not available		6%	**13%**
Insomnia			3%	**7%**
Rhinitis			12%	**18%**
Skin discoloration			1.4%	1.7%

Study 303 – there were no significant differences in laboratory test results between the two arms. Rash rates were 17% in the FTC arm and 14% in the control arm (p > 0.05). Skin hyperpigmentation, isolated to the soles and palms, was more prevalent in black (6.8%) and hispanic (2.9%) patients than caucasians (0%).

Using this information along with that published for the other agents, below is a list of the most common side effects associated with each of the nRTI class of agents. Caution must be used in comparing these as the earlier studied medications may have been prescribed at higher daily dosages (zidovudine), for a shorter period of time (24 weeks vs 48 weeks), or in the presence of co-administered medications with the same side effect profile. It is also important to note that toxicity rates reported from clinical trials are classified by the NIH/NIAID toxicity tables. It is common for the official reporting rates to include only Grade 3/4, the most serious of all events. In real life clinical practice, many patients are not willing to wait until a grade 3 or 4 level toxicity (e.g. diarrhea) before stopping a medication or entire ARV regimen.

Drug	Most common side effects*
abacavir	hypersensitivity reaction, nausea, fever/chills, headache, rash
didanosine	peripheral neuropathy, headache, pancreatitis
emtricitabine	headache, diarrhea, nausea, rash, hyperpigmentation
lamivudine	headache, malaise/fatigue, anorexia, dizziness, nausea, rash
stavudine	peripheral neuropathy, headache, rash, diarrhea, pancreatitis
tenofovir	nausea, diarrhea, vomiting, flatulence
zalcitabine	peripheral neuropathy, rash, pancreatitis, stomatitis
zidovudine	bone marrow suppression, headache, gastrointestinal intolerance, insomnia

* Each agent has lactic acidosis as a potential serious complication of therapy.

It is difficult to predict which patient will have none or all of the side effects associated with a particular agent. Each clinician becomes accustomed over time with the side effects that they feel that they can manage in their patient population and will prescribe ARVs and supportive medication based on this experience.

Precautions/Contraindications

The following precautions and contraindications exist for emtricitabine

a) Contraindicated in patients with a previous history of hypersensitivity to any of the components in the formulation.
b) Lactic Acidosis/Severe Hepatomegaly with Steatosis has been associated with the nRTI class of agents including emtricitabine. The majority of cases have been in women and obesity and prolonged nRTI exposure may be risk factors. *This contraindication is listed for the entire class of nRTI agents.*
c) Post treatment exacerbation of chronic hepatitis B has been seen upon discontinuation of emtricitabine. Chronic hepatitis B infection is not a contraindication to emtricitabine therapy. However, providers should closely monitor clinical and laboratory markers for hepatitis B in the months following discontinuation of emtricitabine
d) Patients with impaired renal function (calculated creatinine clearance < 50 ml/min) require a dose adjustment.
e) All antiretroviral regimens have been associated with fat redistribution and as such all patient should be advised of this potential adverse effect.

Drug Interactions

Emtricitabine has undergone pharmacokinetics analysis with a limited number of co-administered antiretrovirals. When dosed at FDA approved schedules, emtricitabine does not significantly alter the pharmacokinetics of indinavir, stavudine, or tenofovir nor do these drugs alter emtricitabine pharmacokinetics. One additional study has been completed with famciclovir showing no significant interaction. Since emtricitabine is primarily renally excreted, undergoing active renal tubular secretion, it is not expected to interact with the antiretrovirals that are extensively metabolized. As mentioned briefly above, *in vitro* studies indicate that emtricitabine has additive or synergistic activity when used in combination with all other nRTI agents, suggesting that intracellular phosphorylation of the nucleosides is not impacted by the addition of emtricitabine. Only prospective clinical trials using various combinations of these agents will prove whether specific combinations of emtricitabine *plus* one or more other nRTIs are antagonistic.

Acquisition Costs

The FSS drug price as listed on the Amerisource Bergen Online catalog on 7/4/03 is listed below. The cost for emtricitabine was obtained from Gilead Sciences as the price offered to VHA PBM.

Drug	$ per UOU	Qty	Cost/30Day	Cost/pill	Pills/day
abacavir	228.35	60	228.35	3.81	2
didanosine*	172.90	30	172.90	5.76	1
emtricitabine	189.31	30	189.31	6.31	1
lamivudine 150mg	172.06	60	172.06	2.87	2
lamivudine 300mg	183.57	30	183.57	6.12	1
stavudine**	179.48	60	179.48	2.99	2
tenofovir	247.52	30	247.52	8.25	1
zalcitabine	154.96	100	139.46	1.55	3
zidovudine	196.84	60	196.84	3.28	2

*price for VIDEX®EC **price for Zerit® as Zerit®XR not available from prime vendor(7/10/03)

Emtricitabine would be used in conjunction with other ARVs to tailor a treatment regimen. The current DHHS guidelines list the following drug combinations as strongly recommended (in no order of preference): ddI/3TC, ddI/d4T, d4T/3TC, ZDV/ddI, and ZDV/3TC. Emtricitabine might be expected to substitute for lamivudine, another cytosine analogue. Lamivudine is dosed once or twice-daily with the once-daily dose being administered as 1 x 300mg or 2 x 150mg tablets as the 300mg formulation (normal renal function) is not a delayed/sustained release product. A review of VA clinician prescribing of the Epivir® formulation of lamivudine for the first 6 months of 2003 show that over 99% are for the 150mg strength with 95% of the prescriptions using BID dosing in conjunction with other BID nRTIs. For the 5% on QD lamivudine dosing, 83% are using the 150mg strength.

Cost Analysis and Expected Use

In the most recently completed quarter (FY03, Q3), there were 12,261 VHA patients receiving non-investigational ARV therapy according to the National Immunology Case Registry (ICR). Ninety-nine percent (99%) of these patients are receiving at least one drug from the nRTI class. VA clinicians may be inclined to use emtricitabine in place of lamivudine so it is worth looking at use of that medication. Lamivudine, in any of its three product forms, was prescribed to 76% of all patients receiving ARVs in this past quarter. This usage breaks down to 35.7%, 31.3%, 9.9% of patients on any ARV for the three lamivudine-containing products, Epivir®, Combivir®, or Trizivir®, respectively. It is difficult if not impossible to estimate how many of these patients would be switched to emtricitabine or how many patients may be initiated on this medication in place of lamivudine. VA clinicians may decide to switch patients from zalcitabine to emtricitabine therapy although these numbers are small (56 patients on zalcitabine in FY03, Q3). It is also not clear what the role of emtricitabine *vs* other medications used to treat hepatitis B (including lamivudine) would be in the HIV/Hepatitis B coinfected population. Clinical trials evaluating emtricitabine alone and in combination with other anti-hepatitis B medications are underway.

Conclusions

Emtricitabine is a nRTI class antiretroviral approved for use in HIV positive drug naïve and experienced populations in the context of appropriate drug resistance testing. Data for drug experienced patients is derived from switching trials designed to look at the time to virologic failure in virologically suppressed patients. There are no published data on using emtricitabine in

moderately or heavily nRTI pretreated patients with known resistance to some of all of the nRTI class.

Recommendations

Emtricitabine, a cytidine nucleotide analog, is the 8th drug in the nRTI class of antiretrovirals to receive FDA approval. During the drug's development, other drugs in the nRTI class have been approved for once-daily therapy, including another cytidine analog, lamivudine. The nRTI class agents have a wide, drug specific spectrum of toxicities requiring clinicians to choose the correct nRTI backbone for each patient. Emtricitabine is a cytidine nucleoside analog for which there are already two of this class on formulary. One of the formulary agents, zalcitabine, is one of the least potent nRTIs due to dose limiting toxicities and is minimally prescribed in the veteran population. The other, lamivudine, is the most used ARV within VA with 9,289 patients receiving the drug in one of three formulations. Based on available data from clinical trials, emtricitabine is most likely to used as an alternative to lamivudine. Since there are no head-to-head comparative trials with emtricitabine *vs.* lamivudine in patients not already receiving therapy (study GS303 was a switching trial), we can not determine at this time which is the safest or most effective agent of the two. Adverse events from the drug switching trial, where patients where stable on lamivudine, identified some toxicities (headache, insomnia, rhinitis) that may be limited to the initial weeks or months of therapy – something commonly seen with other nRTI class agents. Clinicians should consider and discuss the possibility of skin hyperpigmentation from both emtricitabine and zidovudine with African American and Hispanic patients prior to selecting a new drug regimen. To date in FY 2003, the VHA HIV population is 51% African American and 8% Hispanic.

References:

Published Clinical Trials

Molina, JM, Ferchal F, Rancinan C, et.al. Once-Daily Combination Therapy with Emtricitabine, Didanosine, and Efavirenz in Human Immunodeficiency Virus-Infected Patients. J Infect Dis 2000;182:559-602

Key Presentations (Orals, Posters, Abstracts)

Pharmacokinetics
Wang L, Begley J, Feng, JY et al. Pharmacokinetic and Pharmacodynamic Characteristics of Emtricitabine Support Its Once Daily Dosing. XIV International AIDS Conference. July 7-12 Barcelona 2002 Poster 4546

Clinical Trials
ANRS 031 (MONTANA) – follow up to the JID publication with data out to 24 months
Molia JM et.al. 8th ECCATH, Athens Greece. 2001 Poster #221

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