hi my name is jomie George I am the

pharmacokinetics research lab here at

the NIH clinical Center Pharmacy

Department today Ill actually be going

through a case study focused on

transportermediated drug drug

interactions so lets get started with

the patient case this is a year old

male with a medical history significant

for HIV hypertension and left lower leg

deep vein thrombosis or DVT who presents

to clinic today with a fiveday history

of recurrent nosebleeds and feeling

fatigued his current medications include

the following

the antiretroviral regimen lvidegravir

copassistat tenofovir aliphenamide and

tricidine given as one tablet by mouth

daily the antihypertensive amlodipine

0 milligrams by mouth daily and the

oral anticoagulant used to treat his DVT

provided at 0 milligrams by mouth

twice daily and this started about a

week ago

so when we take a look at this

particular case we need to take a couple

of steps at least to identify the

problem and identifying the problem is

important because we can come up with

logical Solutions on how to actually

best manage these challenges and provide

optimal care for this particular patient

so in looking at whats highlighted in

red

the statement thats provided there

pretty much provides a lot of

information thats extremely important

for management for this patient so this

individual has a medical history that

has a number of comorbidities that

require multiple modalities of drug

therapy which are implicated in a number

of drug drug interactions

also of note whats significant is that

this individual presents with side

effects presumably from his oral

anticoagulant that started about a week

ago

and when we take a look at his his

regimen his medication list

we really need to think about are any of

these particular drugs have clinically relevant drug drug interactions and this is important because this individual is actually presenting with side effects again presumably from his oral anticoagulant when we take a closer look in fact there is actually an interaction between kobasistat which is a PK booster or pharmacokinetic booster or enhancer thats provided as part of his antiretroviral regimen and his oral anticoagulant debigatrin

so our next step is understanding how to go about figuring out what resources we need to use to provide and help support is is there data to support this drug interaction and is this drug interaction clinically relevant and could it possibly explain why this individual has developed this side effect from debigatran and what Ive pulled for you here are two resources that are reputable resources one being the from the University of Liverpool and the second being from lexicomp and these are simple searches that were provided using

their drug interaction Checker online so

if you take a look at these

recommendations theyre actually a

little bit different

however the data that is used to support

these recommendations are similar by the

recommendations provided by University

of Liverpool as you can see here their

recommendation is actually do not

coadminister Medicaid these particular

medications and the data here is to

support it is based on a theoretical

interaction that Kobe assist at can

actually increase the exposure of

debigatrend and well go through the

mechanism of the interaction in a few

slides if we look towards the other side

of the slide where lexicomp provides

also a drug interaction Checker the

actual risk here is not to actually do

not coadminister its actually to

monitor therapy and really look at the

patient and understand the benefit

versus risk ratio and if this there

needs to be any dosage modifications or

avoidance of coadministration

so having said that lets take a look

specifically at the drugs that are

implicated in this particular drug

interaction so kobus is dead as Id

mentioned is a pharmacokinetic booster

or enhancer it doesnt have

antiretroviral properties per se but

its really main focus or function if

you will is to enhance the exposure of

concomitant medications namely the

antiretrovirals that are combined within

the tablet and the bigotran as Id

mentioned is the oral anticoagulant when

you pull data on how these drugs are

metabolized or transported you will note

that Coba cystat actually goes through

sip 0 mediated metabolism specifically

as highlighted here its a strong

inhibitor for sipa as well as a

substrate for it it also inhibits sipd

to some extent but when we take a look

at Transporters and the Transporters

that are implicated for this particular

drug we actually see a number of

Transporters that are involved for this

particular medication including

pglycoprotein bcrp mate

oatpb and b

and these are all different functions

and these Transporters are located all

throughout the body in different in

different areas but whats important to

understand and appreciate is that the

bigotran happens to be a pretty

sensitive substrate for pglycoprotein

the FDA defines a sensitive substrate as

one that in the presence of other

pglycoproteins its exposure will

increase more than twofold so in its

drug development program there is data

for the bigotrend in combination with

other pgp Inhibitors however it has not

been studied with cobisistat so the

natural question again is is this a

clinically relevant interaction and

could this interaction be explaining the

side effect profile for this particular

medication in this patient

so lets take a closer look at the

actual mechanism and really breaking

down what actually is happening what the

picture here is depicting for you is the

uh the intestinal membrane specifically

in the enterocytes where p glycoprotein

is located and Peak liquor protein as

youve learned from the lecture is

located all throughout the body

pglycoprotein is indeed an efflux

transporter and it has its specific

function and role in

mitigating or facilitating a transporter

diffusion across different membranes

so looking at the intestinal membrane

there is an apical side which faces the

intestinal tract or the Lumen the basol

lateral side which faces the blood

now when an individual ingests the

bigotrend in the absence of any

transporter inhibition or induction the

bigotrend sits as a p glycoprotein

substrate

but in the presence of kobasistat

kobusastad actually inhibits this efflux

of dibigatran so essentially Whats

Happening Here is that youve got almost

a stoppage if you will of this

carriermediated efflux and keep in mind

that there is always this constant

concentration gradient that can go from

the apical to the basol lateral side

which really determines the absorption

or the intestinal absorption of a

medication or it can go from the basal

lateral to the apical side which really

determines its excretive gradient

what happens when you inhibit this

particular transport you increase the

concentrations or you actually increase

the intestinal absorption and

bioavailability of oral de bigotran and

what happens you have an accumulation of

the drug within the blood which then

really translates to higher

concentrations higher exposure of the

blood

but again the question is

is this relevant is this exposure high

enough such that this requires a dosage

modification or a recommendation in

avoiding these medications altogether

so Ive pulled for you here the FDA

approved label for de bigatran and Ive

specifically highlighted for you the the

section on drug interactions if you take

a look these labels are actually quite

complicated to go through and as

clinicians wed have to make sure that

were looking at these medications for

the right indication and we understand

what data is available and if that data

can be extrapolated to Other Drugs of

interest and other Target populations

it should be noted that most of the drug

interaction studies that are included

within a drug label are conducted in a

healthy volunteer population and not

within the target population so things

to consider are other patient covariates

that could not that are not actually

accounted for in in the actual clinical

trials so what this section actually

outlines for you are particular

recommendations based on the absence or

presence of the concomitant medication

that could be interacting or interfering

with drug transport it also highlights

for you in the in the presence of kidney

dysfunction or renal impairment if those

recommendations change and specifically

for debigatran the bigotrend is actually

eliminated via glomerular filtration

about 0 percent of it

so from a clinical standpoint this is

actually very very important to

appreciate and to incorporate into our

final recommendation for this particular

patient

so Id like to focus right here where it

says the use of pgp Inhibitors

specifically whats called out our

varampamil amiodarone quinidine

Clarithromycin and ticagrelor all of

these particular medications were

studied with dibigatrend and the

exposure although there were increased

in the presence of these pgp Inhibitors

they were deemed to have a there was a

margin if you will that was of efficacy

and safety within that for for that

particular exposure that was deemed to

be clinically irrelevant or really what

that means is it did not require a

dosage adjustment

but whats important is the next

statement also these results should not

be extrapolated to other pgp Inhibitors

so then the question comes up in this particular case Kobe assist at which happens to be a pgp inhibitor what do you do how do you manage this patient appropriately is it appropriate to continue to dose this individual in the presence of this side effect or do we need to dose adjust perhaps the medication

and this leaved a essentially a research Gap in data and in uh in response if you will to help fill this research Gap there was a publication that was put out by Gordon at Al in circulation in about in 0 which really sought out to help fill this Gap and to study the drug interaction impact of cob assist at on De bigotran I should note here that the study actually looks at this particular interaction in healthy volunteers but this is a comparison between the impact of retonovir which is also a PK booster but this is an older PK booster that has fallen out of favor namely because of side effects and because of the fact that kobuss Dad is now available and is

better tolerated

so this particular study actually looks

at both ratonavir and kobusistat as you

can see here panel a focuses on

ratonavir and panel b or arm B is on cob

assist out these are very simple

concentration versus time curves where

the bigotran plasma concentration is

plotted for you on the yaxis the the

time of administration post the bigotran

administration is plotted for you on the

xaxis both of these arms had three

different phases the first phase in both

arms was to provide healthy volunteers

to bigotran alone the second phase

included providing or giving dibigatran

two hours before either retonovir or

cobesistat and the thought here is that

because this drug interaction is

mediated or modulated by pglycoprotein

perhaps separating their Administration

to mitigate this interaction would help

in perhaps being able to provide these

medications together so that was

actually studied if two hours was

actually enough and if that separation

actually did mitigate that interaction

and that third phase was simultaneous

administration of dibigatran with

ratonavir or Cove assista and as you can

see here you can visually appreciate

that there are significant differences

between both of these arms

particularly in the in the setting of

simultaneous administration of

dibigatran and cobisistat versus

dibigatran and ratonavir you can see a

significantly increased CMax and

overall exposure of the bigotran in the

presence of Cobe assistant

whats interesting though here is that

actually retoniver and Coba system are

both pgp Inhibitors so this actually

speaks to what the label actually

indicates as well that the ability to

extrapolate data to other pgp Inhibitors

may not be appropriate in all patient

populations and this really focuses and

calls out that in the absence of data

extrapolation may not be entirely

appropriate and you need to take a

casebycase benefit versus risk ratio

for each of your your patients

so again even though this PK study

provided quantitative data it provides

you a percentage increase it provides

you metrics as far as how much the drug

is is increased in the in the in the

setting of cob assist at and retonovir

but again the question is is that

exposure increase still clinically

relevant would that put the would this

exposure put individuals at risk for

bleeds namely so in this healthy

volunteer study its apparent that Kobe

did have a much more profound effect as

a pgp inhibitor but extrapolation of

this data may not be entirely

appropriate to all target populations

staggering the dose actually did not

have a an expected pronounced effect it

actually did not mitigate the

interaction and likely the mechanism is

that Kobe is indeed a potent intestinal

pgp inhibitor whereas return of your may

be acting as an inducer a mixed inducer

an inhibitor of piglike protein

the clinical relevance right now at this

moment is really unknown however because

our particular patient is experiencing

side effects this really cannot be ruled

out that possibly the cop assist that is

propagating or perpetuating perpetuating

the the drug interaction with the

bigotran

the therapeutic options for this for

this individual really any individual

based on this PK data is either to avoid

its concomitant use altogether provided

that there is an appropriate alternative

option for the patients second would be

to space apart perhaps the medications

for more than two hours in the case of

debigatran it should be noted that the

bigotran has already been being given

twice a day in this particular patient

and really all patients for the bigotran

is typically dosed twice a day so really

spacing these drugs apart for more than

two hours really doesnt

provide

a chance for patients to be actually

adherent to their medications and

actually could negatively impact

adherence so may not be the the best

optimal Choice and then lastly does it

make sense to reduce the debate Trend

dose but the question then is how much

do you reduce the dose and would that

actually have negative impacts impact

namely on efficacy and remember that

theres a delicate balance between

efficacy and safety this is a drug

thats being given to an individual to

essentially or anticoagulate them after

having identified thrombosis so we do

need to carefully figure out the balance

between efficacy and safety and if that

reduction of dose is truly

therapeutically appropriate

and all for all of those reasons this

really provides or or introduces many

different management challenges Ive

pulled for you here a number of FDA US

product labels for other direct oral

anticoagulants select ones that are

listed here for you riveroxaban apixaban

dibigatran and edoxaban if you look

across the drug interaction potential

actually both River Rocks have been in a

pixel van plausibly actually pose a

higher drug interaction potential

because theyre substrates for both

cytochrome a as well as pglycoprotein

the label recommendations essentially

provide guidance saying that with

riveroxaban drugs like homocystat should

be avoided altogether

apixaban you could use it but you need

may need a dosage reduction depending

upon the indication for the drug and the

patient population and other patient

covariates the bigotran we already went

through the the label recommendation for

that and edoc the band which is a fairly

newer direct oral anticoagulant that

thats available the data actually with

the docs event if you note here for in

the product label is that with specific

pgp Inhibitors you actually might be

able to use it without any dosage

adjustments but I would caution or

advise that we have a patient here

thats developed a side effect plausibly

because of the oral anticoagulant so the

question of being being able to safely

administer in the presence of his
antiretroviral regimen really should be
questioned and Im not entirely sure if
really switching him to a docs event
would be the most appropriate option
but having said that we have to do
something for our patient we have to
make a decision so we do we did identify
the the relevant drug interaction were
essentially deeming this to essentially
be clinically relevant for this
particular patient case as hes
developed side effects presumably from
his debigatran and because hes feeling
fatigued remember he could have lost
actually quite a bit of blood but we
dont have other laboratory markers to
really support that but really it it
should cause concern given that he has
had recurrent nosebleeds really
temporally associated with the time of
initiation of his debugatran
and really what we need to do is to
think about and ask advice from
Specialists and really take a multi
multidisciplinary approach in really

managing this particular patient so

really it would be great to work with

the his HIV provider to discontinue his

Cove assist at based antiretroviral

therapy and really construct an

alternative regimen which poses a much

lesser drug interaction risk and in this

situation you could actually continue

his debugitran and treat him for his DVT

or

other options could potentially be if

for whatever reason he cannot tolerate

or cannot be switched to an alternate

alternative antiretroviral regimen we do

need to think about switching him to

another oral anticoagulant but would

need very frequent monitoring to ensure

that he doesnt continue to have side

effects from his oral anticoagulant

so in summary drug Transporters are

implicated in many clinically relevant

drug interactions it may not be

appropriate to extrapolate drug

interaction data generated from healthy

volunteers to a Target population or

rather for a drug of Interest other

drugs of Interest it is important to

practice a multidisciplinary approach

in the management of these patients who

do present with rather complex

comorbidities which end up having very

complex drug drug interactions thank you

and I hope this presentation was helpful