ORIGINAL ARTICLE

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Calcaneal Quantitative UltraSonometry (QUS) in HIV-1 positive subjects

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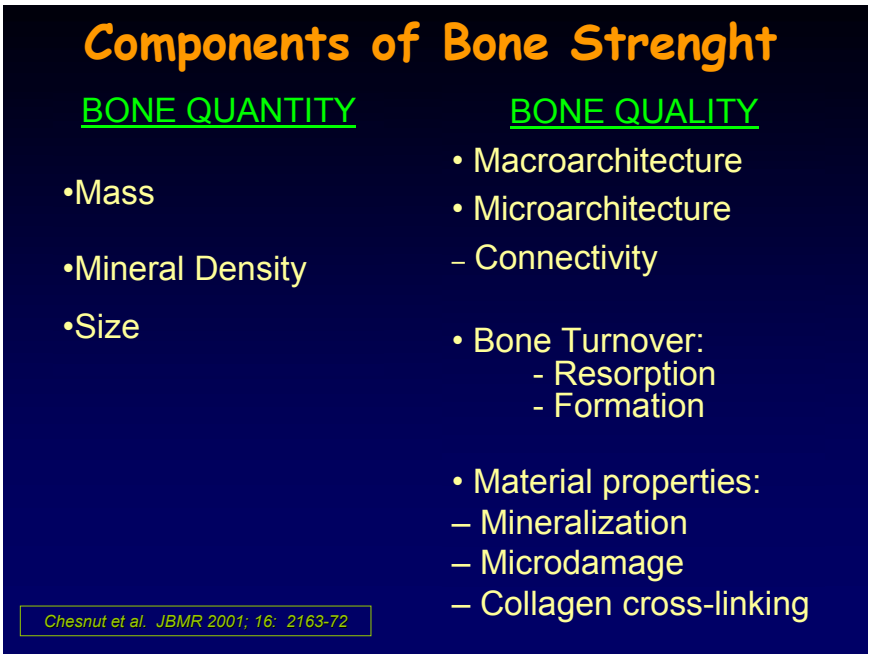
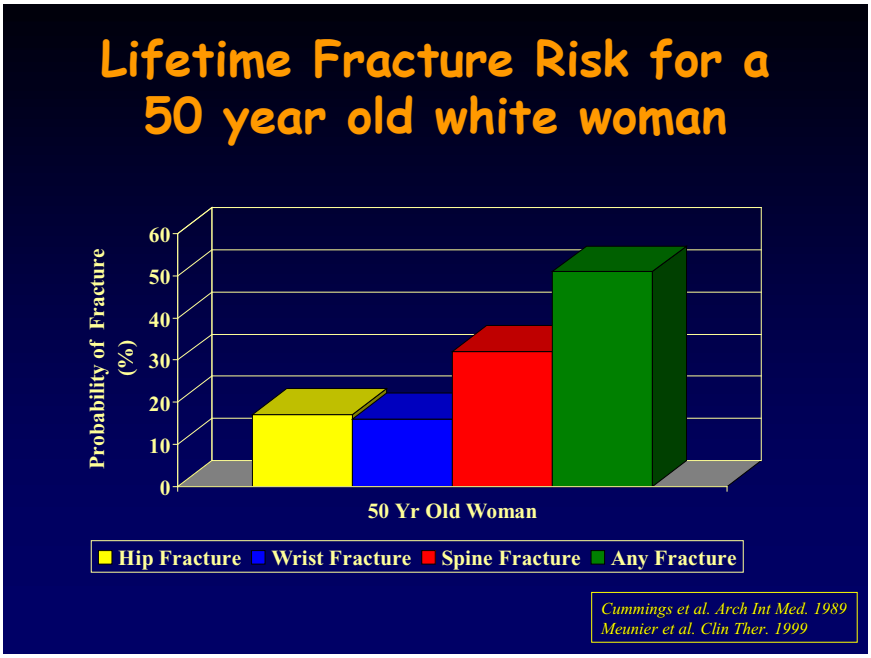
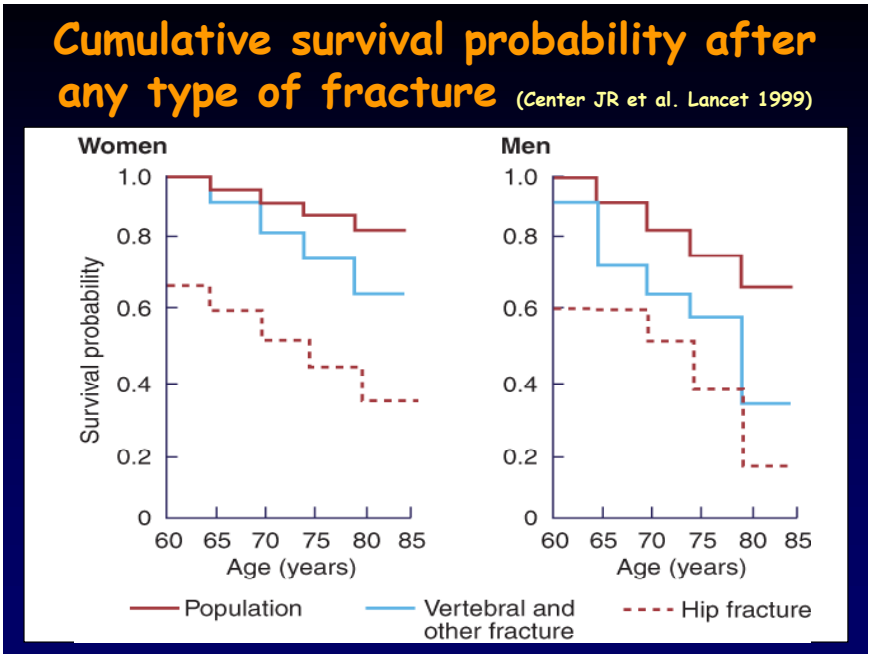
Osteoporosis is a systemic disease characterized by a decrease in bone strength, defined as an integration of two elements: bone quality and bone quantity.



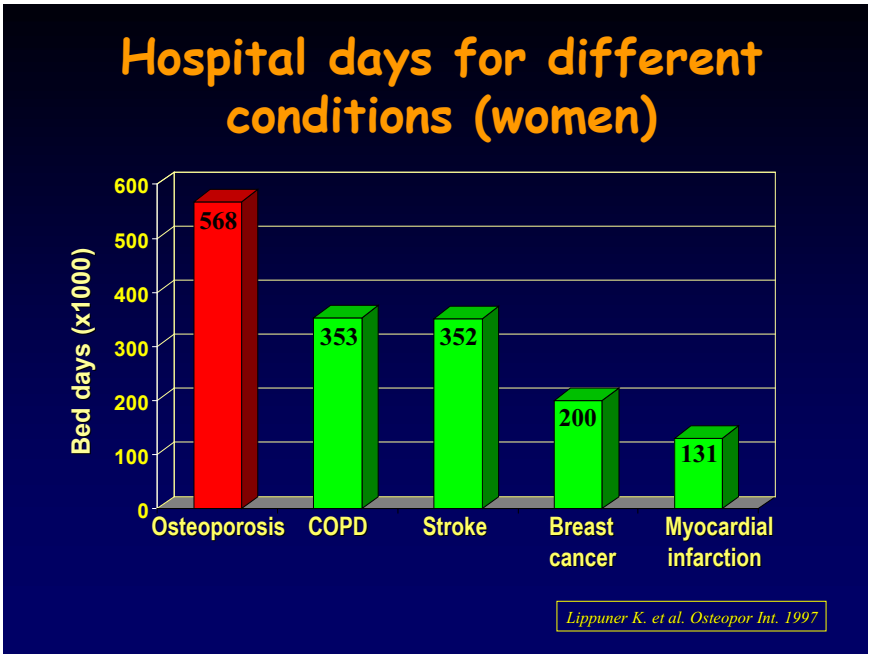
This condition leads to enhanced bone fragility and to a consequent increase in fracture risk.
The classic risk factors for osteoporosis include: hypogonadism, family history of fractures, BMI<19 kg/m^2, hypovitaminosis D, smoking, sedentary life-style, low impact fractures, advanced age, female gender, menopause and/or amenorrhea, habitual alcohol consumption of >3 units/day, steroids exposure for >3 months.
Osteoporosis is a major public health problem and it affects approximately 14% of man over 65 years and 23% women over 40 year, leading to more than 300.000 hip fractures annually (1).



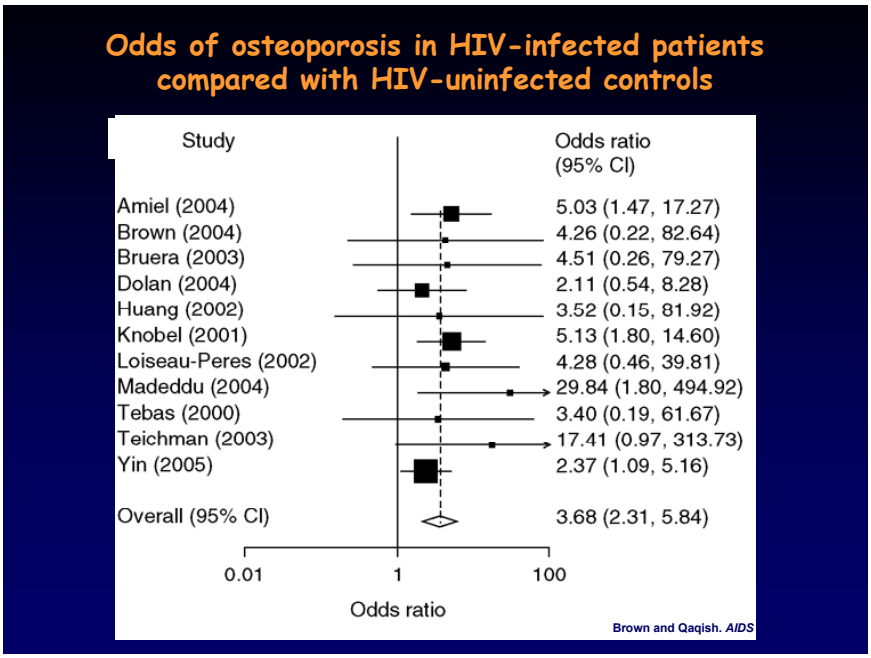
The associated mortality rates are 37 and 45 % for hip and vertebral fracture, respectively (2).



Therefore, with the progressive aging of population in developed countries, osteoporosis represents one of the major health problems in the elderly (3) and imposes considerable economic burden on the health care system in terms of hospital costs and motor disabilities.

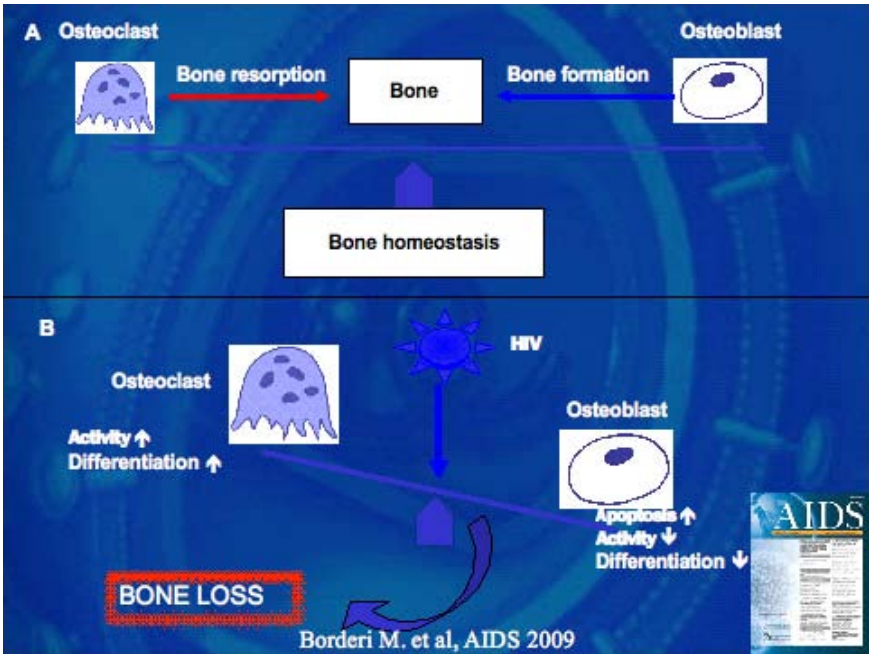


The main objective in the management of osteoporosis is to avoid fractures, operating with a preventive approach in an early phase of the disease.
HIV-infected subjects deserve particular attention.
They show several bone lesions correlated with the development of infection and osteopenia and osteoporosis are the most common of these.
A meta-analytical review of cross-sectional studies published in the period 1996-2005 shows an overall prevalence of osteoporosis of 15% in an HIV-infected population with an average age of 41 years and a 3.68-fold increased risk of osteoporosis compared with their HIV-uninfected counterparts (4).

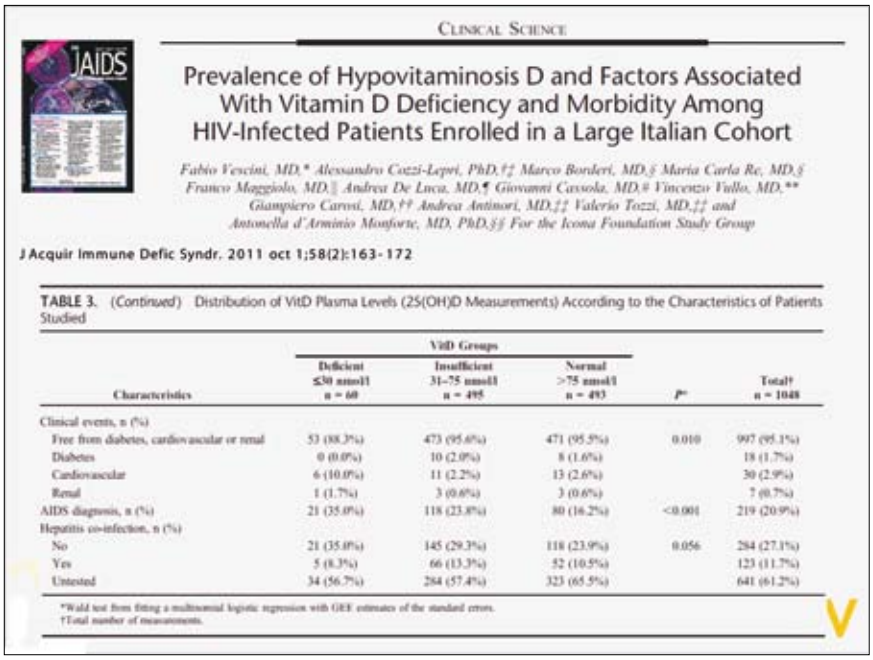


Further, a study in the Massachusetts General Hospital/Partners Healthcare System involving 8528 HIV-infected persons and more than 2 million HIV-uninfected persons showed a substantially increased prevalence of fracture in HIV-infected persons (5).

The reduction in bone mineral density is a proved metabolic complication of HIV and of its treatment and several causing mechanisms should be taken into account.
A pathogenetic role is identified in the infection itself and viral replication is considered a factor of BMD loss, because HIV activates osteoclast cells and leads to osteoblast's apoptosis.



Moreover, antiretroviral therapy (ART) affects bone metabolism in different ways, compromising osteoclast-osteoblast balance or inducing mitochondrial toxicity.
Therefore, HIV infection has to be considered a cause of secondary osteoporosis.
A detailed history and physical examination allow the physician to investigate main osteoporosis risk factors, to whom add nadir LyT CD4+ value, HIV-RNA, protease inhibitor plus tenofovir use.
In addition, vitamin D deficiency and consequent secondary hyperparathyroidism are more frequent in HIV-infected patients, leading to bone reabsorption, especially in the femoral neck.


CLINICAL SCIENCE

JAIDS

Prevalence of Hypovitaminosis D and Factors Associated With Vitamin D Deficiency and Morbidity Among HIV-Infected Patients Enrolled in a Large Italian Cohort

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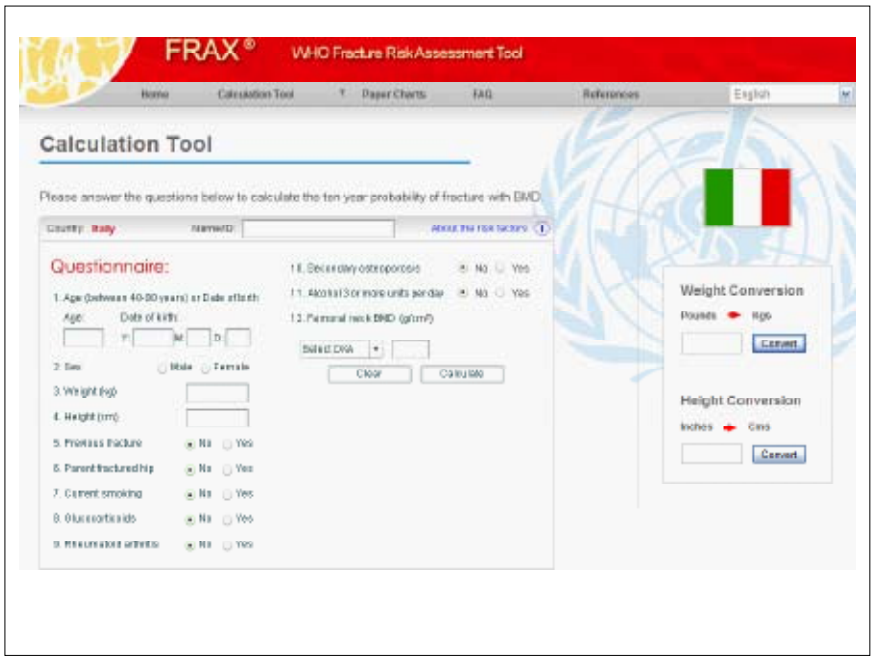
TABLE 3. (Continued) Distribution of VitD Plasma Levels (25(OH)D Measurements) According to the Characteristics of Patients Studied

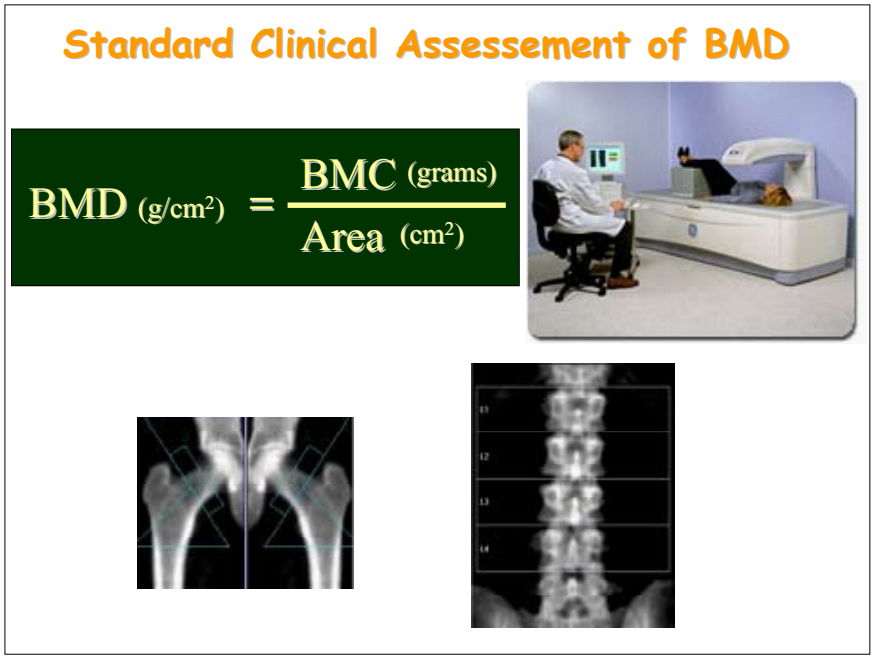
Characteristics	VitD Groups: Deficient ≤30 nmol/l n = 60	Insufficient 31–75 nmol/l n = 495	Normal >75 nmol/l n = 493	P*	Total† n = 1048
Clinical events, n (%)					
Free from diabetes, cardiovascular or renal	53 (88.3%)	473 (95.6%)	471 (95.5%)	0.010	997 (95.1%)
Diabetes	0 (0.0%)	10 (2.0%)	8 (1.6%)		18 (1.7%)
Cardiovascular	6 (10.0%)	11 (2.2%)	13 (2.6%)		30 (2.9%)
Renal	1 (1.7%)	3 (0.6%)	3 (0.6%)		7 (0.7%)
AIDS diagnosis, n (%)	21 (35.0%)	118 (23.8%)	80 (16.2%)	<0.001	219 (20.9%)
Hepatitis co-infection, n (%)					
No	21 (35.0%)	145 (29.3%)	118 (23.9%)	0.056	284 (27.1%)
Yes	5 (8.3%)	66 (13.3%)	52 (10.5%)		123 (11.7%)
Untested	34 (56.7%)	284 (57.4%)	323 (65.5%)		641 (61.2%)

*Wald test from fitting a multinomial logistic regression with GEE estimates of the standard errors.
†Total number of measurements.

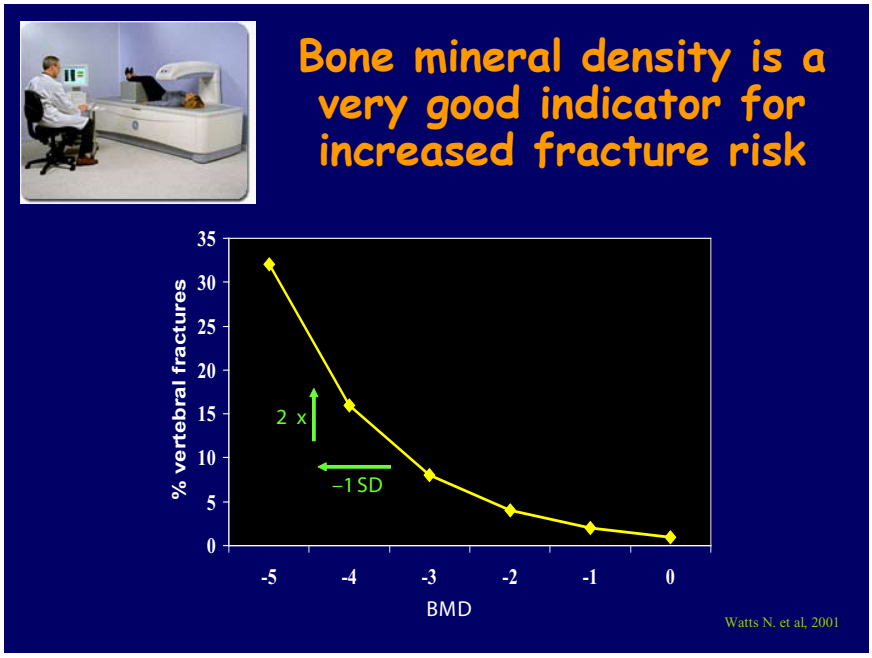
Fractures are the clinical complication of osteoporosis and are defined as those occurred with minimal trauma such as fall from standing height or less, including any type of fracture.
There are some useful clinical tools to estimate the 10-years probability of bone fracture risk, such as FRAX (6, 7) and Qfracture (8).
FRAX score can calculate the 10-year probability of a fracture in patients with osteopenia/osteoporosis age 50 and older but there are insufficient data to validate its utility in HIV-patients, where the risk can be underestimated (9).



Nevertheless, at present, the gold standard for the diagnosis of osteoporosis is the measurement of bone mineral density (BMD), assessed by dual-energy X-ray absorptiometry (DXA).
According to WHO definition, the BMD value is expressed in terms of numbers of standard deviation from the mean BMD of a healthy young adult reference population (T-score) and osteoporosis has been defined by a T-score of 2.5 or less (10).
Until 2013, the National Osteoporosis Foundation guidelines did not include HIV infection and highly active antiretroviral therapy as osteoporosis risk factors that should trigger dual-energy x-ray absorptiometry (DEXA) screening for low bone mineral density (BMD) in older adults.

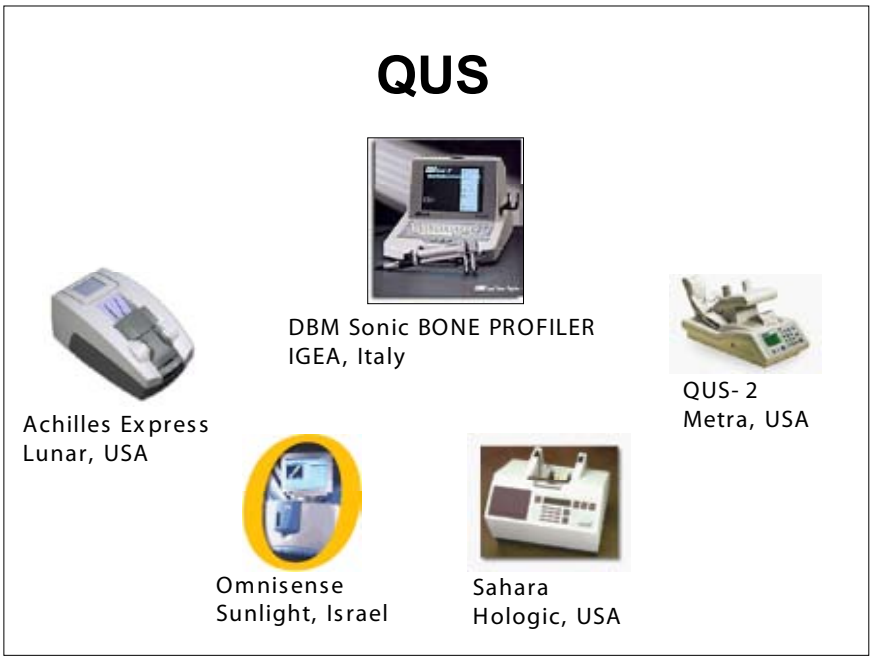


At present, DEXA screening is recommended in HIV-infected men older than 50 years and HIV-infected postmenopausal women. In general, guidelines for treatment of low BMD in HIV-infected patients are the same as those established for the general population. It is important to consider secondary causes of low BMD, particularly vitamin D deficiency and phosphate wasting.
The absolute risk of fracture should be used to help guide decisions in management and treatment (11).

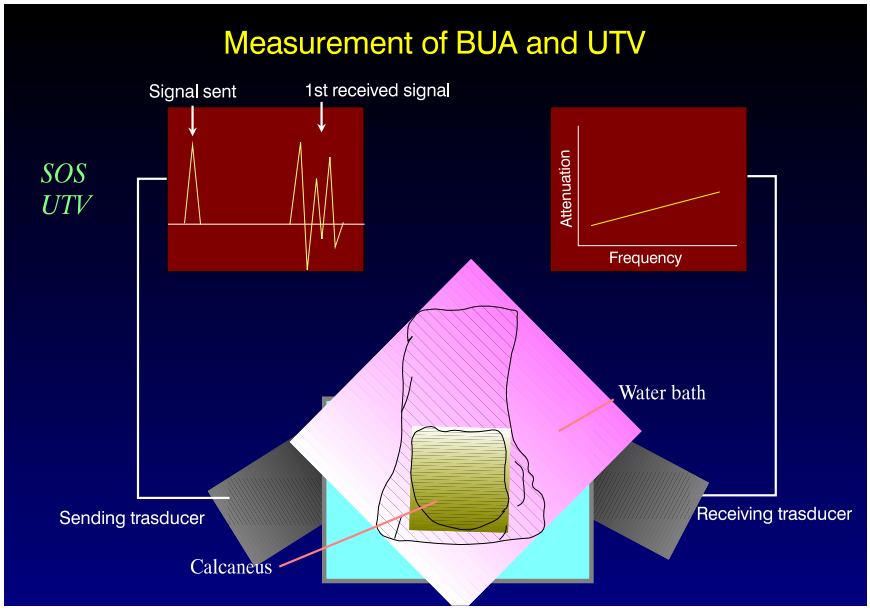


Although BMD is the standard method for bone assessment, it is not a complete and perfect predictor. WHO definition is able to describe the low bone mass (bone quantity) that characterizes an osteoporotic skeletal condition, but it lacks information about the microarchitectural deterioration of bone (bone quality).
Moreover, a large number of subjects at risk remains undiagnosed, due to the relatively high cost and a poor accessibility of DXA device in certain geographic parts of the world (12, 13).

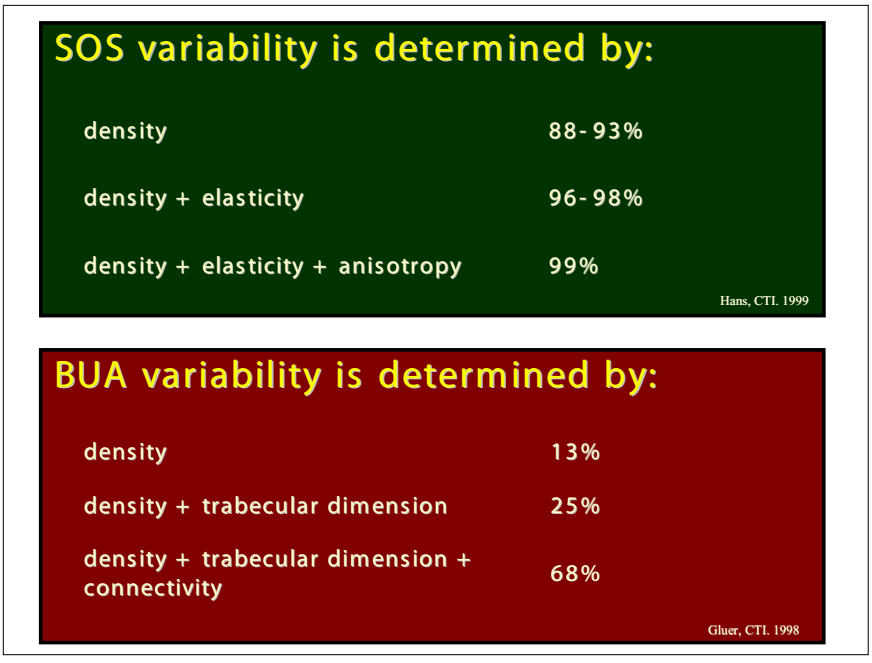
To overcome these limitations, Quantitative UltraSonometry (QUS) has been introduced, an alternative technique useful to provide information about both bone density and bone structure.



The ultrasound is a type of sound wave with a frequency exceeding the normal auditory range of humans (>20 kHz).
The frequency used in QUS usually lies between 200 kHz and 1.5 MHz.
The sound waves produced by unique piezoelectric probes are emitted and travelled longitudinally or horizontally through the bone under study.
There are usually two probes on the QUS device: the emission and receiver probes.
The segment of bone under study will be placed between these probes and the ultrasound waves emitted from the emission probes through the bone will be sensed by the receiver probe.
There are two types of QUS depending on the axis the ultrasound waves take to travel through the bone. Horizontal transmission uses probes that measure the speed of sound on the cortical layer of the bone at a fixed distance.
The segments of bone measured as such are the forearm, tibia and radius.
Longitudinal transmission is more often used and the bone segment measured is the calcaneus.
According to the International Society of Clinical Densitometry (ISCD), calcaneal QUS is the only recognized measurement of QUS as the determinant of bone health status because more research has been performed on the calcaneus as compared to the other bone segments.
Besides, the calcaneus consists of 95% trabecular bone and possesses two lateral surfaces, which facilitates the movement of ultrasound through it.

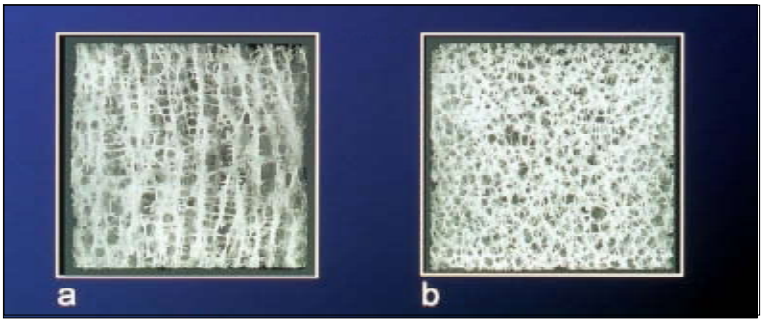


QUS is a non harmful, portable and fast technique, able to assess bone structure, porosity and trabecular orientation.
QUS does not measures BMD but rather broadband ultrasound attenuation (BUA - decibels per megahertz), speed of sound (SOS - meters per second) and stiffness index (SI) at the hell, tibia, patella and other peripheral skeletal site.
The speed of sound refers to the division of transmission time of the sound waves by the length of the body part studied. The unit used in the measurement of SOS is meter per second (m/s).
Broadband attenuation of sound refers to the slope between attenuation of sound signals and its frequency, and the unit used is dB/MHz.
Attenuation occurs because the energy is absorbed by the soft tissue and bone when the sound waves travel through them.
Currently, more sophisticated QUS indices derived from these two basic measurements are available, such as amplitude-depend SOS (AD-SOS), stiffness index (SI), quantitative ultrasound index (QUI) and estimated BMD (eBMD).



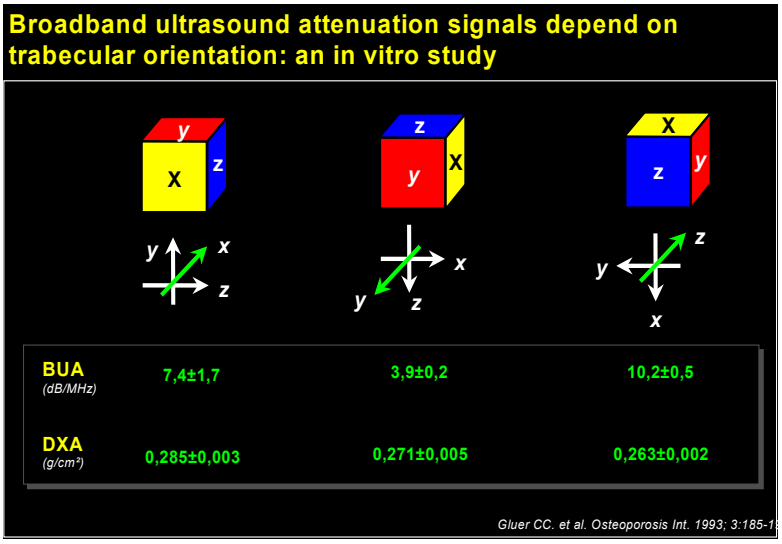
Previous in vitro studies examining the relationship between calcaneal QUS and bone properties found that SOS was closely related to BMD.
Toyras et al. indicated that this relationship was strong, with a coefficient of correlation (r) of 0.888. Significant correlations between SOS with microarchitecture indices of the bone, such as bone volume (BV/TV), bone surface (BS/TV), number of nodes (N.Nd.), trabecular number (Tb.N.), trabecular thickness (Tb.Th.) and trabecular separation (Tb.Sp.) were also discovered.
There were opinions that these correlations were mediated by the bone mass, and if BMD was controlled, these relationships would revert to become non-significant.
However, a computer simulation study performed by HaÏat et al. showed that after adjusting for BMD, BV/TV remained significantly associated with SOS.
This was confirmed by later studies using excised samples, whereby microarchitecture of the bone was significantly associated with SOS and contributed to the variation of SOS apart from BMD.
Bone biomechanical studies revealed that Young's modulus, compressive modulus, ultimate strength and elasticity of bone were significantly associated with SOS.
Cavani et al. indicated that the combination of bone density and Young's modulus could explain 93.34% of the in vitro variation of SOS.
Studies also showed that BUA was significantly associated with biomechanical parameters, but Toyras et al. indicated that this was only true in low-density bone samples. In high-density bovine samples, BUA failed to predict BMD and biomechanical strength.
These in vitro experiments showed that QUS indices are able to reflect the two principal constituents of bone health, which are the bone quantity (BMD and bone mass) and the bone quality (bone microarchitecture and strength).

The lateral (a) and the superior- inferior view (b) of a vertebral (L4) cube



The stronger association between QUS indices and BMD indicates that bone quantity contributes to most of the variation in QUS.
In humans, there were significant correlations between QUS indices and BMD values at various body sites assessed cross-sectionally.
Dane et al. reported that all three QUS indices, BUA, SOS and SI were significantly correlated to BMD at lumbar spine and femur in postmenopausal women, but only SOS correlated significantly to BMD at lumbar spine and femur in premenopausal women.
In a study by Mészáros et al. in men, BUA correlated significantly and moderately with BMD at lumbar spine, femoral neck and radius midshaft.

However, SOS did not correlate with the BMD at the aforementioned sites.
In a longitudinal study by Trimpau et al. involving 80 Swedish women aged 53-73 years, BUA and SOS were significantly correlated with BMD at multiple skeletal sites at the first screening and the after seven years later.
Furthermore, the changes of DXA and QUS measurements during the follow-up period were also significantly correlated.



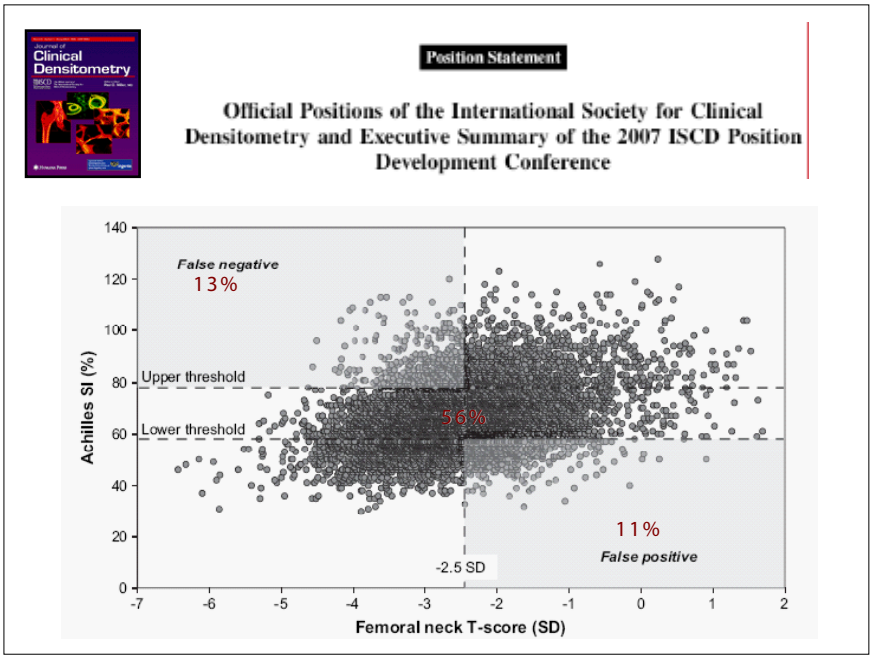
The ability of QUS to predict fractures were also validated in several human cohort studies.
Hernandez et al. examined 5195 Spanish postmenopausal women ≥ 65 years and found that all QUS indices (BUA, SOS, eBMD and QUI) were significantly different between subjects with and without history of fractures.
Logistic regression analysis also confirmed that these QUS indices were significantly associated with previous fractures. Similar findings were also found in men.
The study of Varenna et al. in 4832 Italian men aged 60-80 years found that QUS indices (BUA, SOS, SI) were significant associated with history of hip fracture and non-spinal fracture.
These observations from cross-sectional studies were further validated by prospective studies.
In the Norfolk Cohort Study involving 14824 men and women aged 42-82 years followed for 1.9 years, Khaw et al. discovered that one SD decrease in ultrasound velocity translated to a 60% increase in fracture risk in both genders.
They also found that the risk increased for older subjects and doubled for subjects with history of fractures.
In the Asian population, Fujiwara et al. showed that SOS, BUA and SI significantly predicted hip, wrist and non-spinal fractures in Japanese men and women followed for 5 years.
In a recent meta-analysis, Moayyeri et al. concluded that SOS, BUA, SI and QUI significantly predicted fractures after reviewing 21 independent studies
In addition, QUS is not associated with any radiation exposure and it is less expensive than DXA, so it is applicable and acceptable in epidemiology studies, especially in undeveloped areas and developing countries.
Cournil et al. showed this ability of QUS in a resource-limited setting as Dakar, Senegal (14).
In this study a Pegasus Prestige ultrasonometer was able to reveal in HIV-infected patients on antiretroviral therapy a lower BUA measurement than their uninfected counterparts, highlighting a skeletal condition otherwise no estimable with DXA.
Cross-sectional and prospective studies proved the ability of QUS parameters to discriminate subjects at risk of fracture (15-17), even better than DXA.

DXA and QUS in the prediction of vertebral fractures Study
Population: 500 postmenopausal women (65- 75 yrs)

Variable	ORs (95% CI)	AUC
Achilles BUA	2.7 (1.5-4.8)	0.76
Achilles SOS	2.8 (1.5-5.2)	0.74
Achilles Stiffness	3.0 (1.6-5.6)	0.76
Bone profiler AD-SoS	2.1 (1.3-3.4)	0.72
Bone profiler UBPI	2.2 (1.1-4.4)	0.71
DXA lumbar spine	2.1 (1.2-3.9)	0.70
DXA neck	1.9 (1.0-3.3)	0.66
DXA trochanter	2.7 (1.5-4.8)	0.75
DXA total hip	2.4 (1.3-4.3)	0.72

Hartl F et al., JBMR 2002

Therefore, QUS of the heel has been proposed as a screening tool to evaluate the bone status and the risk of osteoporotic fragility fractures.
Validated heel QUS devices predict fractures in postmenopausal women (vertebral, hip and overall fracture risk) and in men 65 and older (hip and non-vertebral fractures).
Cross-sectional studies in the literature and two main prospective studies, Epidemiology of Osteoporosis (EPIDOS) and the Study of Osteoporotic Fractures (SOF), demonstrated how heel QUS can discriminate as well as BMD by DXA between patients with fractures and those without.
However, the combination of QUS variables and BMD did not increase fracture discrimination (18).
In a longitudinal study by Chan et al., the combination of BUA and femoral neck BMD predicted hip, vertebral or any fractures better than individual indices in postmenopausal women but not in men followed for 13 years.
In cross-sectional studies by Mészáros et al. and Gonnelli et al. involving male subjects, both SOS and BUA were able to discriminate subjects with fractures from those without.
Both studies also revealed that SOS had better or the same discriminatory ability than BMD. On the other hand, some studies reported that BMD had better discriminability than QUS, and the combination of DXA and QUS did not improve predictability.
A study by Kwok et al. in 1921 Hong Kong Chinese men followed for 6.5 years demonstrated that BUA, QUI and BMD (hip and spine) significantly predicted major fragility fractures and non-vertebral fractures, but BMD was better in predicting the former.
In addition, the combination of BMD and QUS did not improve fracture predictability.
El Maghraoui et al. reported that only lumbar spine BMD predicted vertebral fractures in postmenopausal women but QUS did not.
Dane et al. showed similar results in pre- and postmenopausal women in their study.
In view of the heterogeneity of the results on the comparison, a meta-analysis was performed by Marín et al.
It was revealed that the predictability of QUS in non-spinal fractures was similar to DXA, but DXA was more superior in predicting hip fractures.
Unfortunately, no clinical guidelines for QUS in osteoporosis have been developed or widely accepted and very few studies have validated its utility in HIV+ patient's management.
In 2007 The International Society for Clinical Densitometry (ISCD), during a Position Development Conference (PDC), stated the clinical applications of QUS for fracture risk assessment, the diagnosis of osteoporosis, the treatment initiation and the monitoring of treatment (19).



For this document, the only validated skeletal site for the clinical use of QUS in osteoporosis management is the heel and QUS measurements from different devices cannot be directly compared.

According to a large body of evidence, validated heel QUS devices are able to predict fragility fracture in post-menopausal women (hip, vertebral and global fracture risk) and man over the age of 65 (hip and all non vertebral fractures), independently of central DXA BMD (20-22).

Osteoporosis cannot be diagnosed by QUS according to the WHO classification, because it has been validated only for DXA technology.

To identify patient at high or low risk to have osteoporosis, The ISCD Official Position defines specific thresholds deduced from data published by Hans et al (23, 24).

The upper thresholds for Stiffness Index are 83 units and 78% for the Sahara and the Achilles devices respectively and the corresponding lower thresholds are 59 units and 57%.

Even if many in vivo and in vitro studies have demonstrated the strong correlation between QUS and BMD in trabecular bone (25, 26), central DXA measurements at the spine and femur remain the preferred method for taking therapeutic decision.

Moreover there are no randomized clinical trials showing reduction of fracture risk in patient selected for treatment according only to QUS measurement.

However, heel QUS may help to determine therapeutic strategies by associating these thresholds with the valuation of clinical risk factors (CRFs).

According to meta-analyses and reviews published by Kanis and Durosier (27, 28), the main CRFs to use in a decision model are: age over 75 yr, low BMI, previous fracture after 50 year, maternal history of hip fracture, current smoking, diabetes mellitus, ever use of glucocorticoids, fall within the last 12 months, use of arms to stand up from a chair.

Hans and Durosier developed a hip screening tool that combines the result of a relevant clinical risk factors (CRFs) assessment and a calcaneal QUS Z-score, to determine the 10-year probability of hip fractures in elderly women.

Realizing a 10-year fracture prediction model, the authors demonstrated that the probability of a fragility fracture increases with the number of CRFs and with a decreased stiffness index (29-31).

The five CRFs included in the model were diabetes, a history of fracture, a history of at least one fall over the preceding 12 months, results of the chair test and current cigarette smoking.

Then, they calculated the probability of fracture for each woman (high, moderate or low) and established high- and low- risk thresholds, defined as the probability related to a given value of SI in the absence of any of the 5 CRFs.
Moreover, the prediction model reaches the aim to improve the time point.
Indeed, while the WHO classification of osteoporosis is based on DXA measurement at baseline, the probability model estimates what will happen in 10-year time.
According to the official position of ISCD on QUS bone assessment, several aspects concerning the use of T-score, reference range, precision and inter-device comparison were addressed.
In the classification of low bone density using DXA, T-score with cut-off points of ≤ -1.0 SD for osteopenia and ≤-2.5 SD for osteoporosis are used.
However, the use of the same cut-off points in QUS measurement is not recommended because QUS and DXA essentially employ different technology in assessing bone health.
Several studies also showed that simply applying the conventional DXA cut-offs in QUS measurement significantly underestimates the true prevalence of osteoporosis.
A number of cut-off points for bone health classifications for QUS had been suggested previously, but they were specific to the device used.
As an example, Frost et al. reported that T-score cut off values for osteoporosis were -1.61, -1.94 and -1.90 for BUA, SOS and eBMD measured using Hologic Sahara ultrasonometer, and -1.45 and -2.10 for BUA and SOS measured using Osteometer DTUone.
The use of an appropriate reference range is important for accurate classification of bone health using QUS and DXA.
For example, a Caucasian reference range, where bone density outcomes are typically higher than Asian bone density outcomes, will eventuate in Asian subjects being classified as having low bone density.
Chin et al. reported that even the use of references from different Asian countries caused significant discrepancies in the classification of subjects with low bone health.
The normative values for different populations around the world had been generated for various QUS devices.
Both the population of interest and the device used should be considered when incorporating the respective normative values in QUS device.
Due to the fact that numerous QUS devices have been developed by many manufactures, each with its own designed logarithm for the calculation and interpretation of QUS indices, inter-device comparison of the results of bone health assessment is not advised.
The precision of QUS devices was reported to be poorer compared to DXA devices.
This may be one of the reason QUS devices are not recommended for patient follow-up in the treatment of osteoporosis unless DXA is inaccessible.
The precision values of SOS and BUA are different due to the effect of a large denominator of the former, hence SOS tends to have smaller precision values.
Examples for precision values reported for the CUBA McCue instrument were 2.4% for BUA and 0.3% for SOS.
Many authors suggest that for the use of QUS in the screening of bone health in local community, an ultrasonometer validated against DXA should be used.
The ultrasonometer should also be equipped with the local reference curve (or a reference curve from a population with the most similar background) for the purpose of bone health classification.
Short-term and long-term in vivo precision of the device should be established for the purpose of the follow-up of subjects.
The papers by Bonnick et al. and Gluer et al. should be referred for steps to establish the precision values.
Furthermore, QUS results should be interpreted with clinical risk factors for maximal detection of subjects with osteoporosis.

The clinical utility showed by QUS in the management of osteoporosis is the possibility to identify patients at high risk who should initiate a treatment and subjects with a sufficient low probability of osteoporotic fracture that require no further medical investigation.

At present, there are few studies evaluating the effects of pharmacological treatment on QUS parameters, so it is not recommended for monitoring treatment efficacy.

The clinical ability of calcaneal stiffness index to screen for osteoporosis HIV-infected individuals was recently demonstrated by Scourfield et al., in which study the use of QUS has avoided 43 unnecessary DXA scans, missing 19 cases of osteopenia and with, most important result, no missed cases of osteoporosis (32).

Navarro et al. evaluated the ability of QUS as a screening tool to discriminate the risk of vertebral fracture in post-menopausal women, avoiding to perform unnecessary DXA in subject at low risk (33). The aim of this study was to define threshold values that would maximize the predictive ability of QUS to discriminate subjects with vertebral fractures using the classification and regression trees (CART) models. A cross-sectional analysis was made of a cohort of 1,132 caucasian post-menopausal women with a mean age of 58 years and all subjects underwent calcaneus QUS measurement, using the Sahara Clinical sonometer.

As previously described (17, 34, 35), patients who sustained a vertebral fracture showed lower values of both DXA and QUS measurements.

However, postmenopausal women with QUI values >90.5 have a low risk of suffering from vertebral fractures and these women could be excluded from DXA evaluation.

In conclusion, Navarro showed that a value of QUI >90.5 is associated with a very low risk of vertebral fractures, with a sensitivity that may reach 80.3 % and a negative predictive value as high as 94%.

These results are slightly different from the ISCD position statement, due to different methodologies.

Studies about the usefulness of QUS in assessing nonvertebral fracture risk were conducted by Liu et al. (36, 37).

In a cross-sectional, population-based study conducted in Shanghai, a total of 9352 Chinese women

and men aged 40 and older underwent calcaneus QUS measurement with Achilles Express device.
The authors proved that for each standard deviation reduction in QUS variables, there was a nearly 1.5-fold increase in nonvertebral fracture risk after adjustment for gender, age, BMI, smoking, alcohol consumption, menstrual status and years since menopause.
Therefore, as a screening tool, the SI-derived T-score obtained from the Achilles QUS device for a postmenopausal woman or man that is less than >1.25 and >1.30, respectively, may indicate an increased risk of osteoporotic fractures and should be further evaluated by central DXA.
The sensitivity of these cut-points was in the range 76-85%, whereas the specificity was much lower, indicating that this heel QUS device can only be used as a screening tool, which stresses sensitivity over specificity, rather than a diagnostic test.
To extend the usefulness of QUS as a screening technique for osteoporosis in HIV-positive individuals, Seyler et al. have recently demonstrated that this device could represent a screening alternative to DXA also in this population of patients (38).
DXA (hip) and calcaneal QUS GE-Achilles Insight (GE-AI) were performed in 105 HIV-negative individuals and, using DXA as gold standard, the sensitivity and specificity of QUS resulted 78% and 84%, respectively.
The PPV and NVP were 32% and 97,5% , respectively, highlighting that QUS is reliable in excluding the presence of osteoporosis.
Authors conclude that these results warrant the evaluation of QUS as a screening tool in HIV-infected patients, to save a substantial number of DXA scans.
Different results have been obtained by De Wit et al., which performed GE-AI and DEXA in a cohort of caucasian and africans HIV patients aged 50years or more (39).
In comparison to DXA, GE-AI was an inadequate tool to detect osteopenia/osteoporosis in this HIV-population for a low sensitivity (64%) and a limited specifity (84%).
Discrepancies between the two methods could not be explained by any of the following variables: age, race, gender, BMI, current CD4+, nadir CD4+, duration on cART, cART regimen, smoking status, alcohol intake, physical activity, personal and family history of fracture, daily calcium intake, vitamin D supplementation, oestrogen intake.
Discordant results between heel QUS and central DXA are not infrequent, due to the difference of these two techniques.
Many authors found that the relationship between QUS parameters and incident fractures may be independent of the BMD assessed by DXA (21, 40-43).
Moreover, a study has found that approximately 50% of women and 70% of men with fracture occurred with BMD level above the WHO defined osteoporotic range (44).
To better explain the occurrence of fragility fracture in individual with high BMD, Chan et al. tested broadband ultrasound attenuation (BUA) at the calcaneus, using CUBA sonometer, among women with BMD T-score>2.5 (45).
His results suggest that decreased BUA and low calcaneal stiffness index are significantly associated with greater fracture risk in women with BMD T-score above -2.5 at femoral neck.
Consequently, calcaneal QUS can be considered an independent predictor of fracture risk in women with non osteoporotic BMD and it could help to identify additional high risk individuals, non diagnosed with DXA.
This finding is in line with previously reported EPIDOS study, which aimed to identify factors associated with hip fracture in women with high BMD.
A probable explanation for the stronger association between BUA and fracture risk in these women

could be attributed to the capacity of QUS to value both bone quantity and bone quality.
Thus, QUS device provides additional information about bone elasticity and microarchitecture, which are important determinants of bone strength (46).
Furthermore, Chan et al. underlined how BUA measurement could individualize the risk of fracture and the relative treatment.
In fact, the association between BUA and fracture risk in men didn't reach statistical significance using the same cut-off value of BMD T-score of women to define osteoporosis, while BUA was found to be significantly associated with greater fracture risk in men when the cut-off value was increased to -1.
Since man have larger bone size and higher BMD measurements than women, using the same BMD cut-off value there is the risk to classify more man as non-osteoporotic, while QUS parameters are able to discriminate these structural differences.
Although the high correlation between QUS and BMD in trabecular bone has been confirmed and it is well understood, the situation and the management with cortical bone are different, because non heel QUS device have not been validated and data are lacking.
In conclusion, heel quantitative ultrasound is proven to predict hip fracture risk and vertebral fracture in post-menopausal women in general population.
Although more evidence are necessary, calcaneal stiffness index is a reliable and cost effective method to also screen HIV- infected subjects for osteoporosis.
The Italian guidelines for the management of HIV infection recognize clinical utility of QUS to predict fracture risk as it allows in post-menopausal women to screen subjects at risk of osteoporotic fracture, needing a DXA scan (47).

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